CITIZEN PETITION
TO THE FOOD & DRUG ADMINISTRATION
TO PROTECT PUBLIC HEALTH FROM UNSAFE USES
OF ANTIBIOTICS IN LIVESTOCK & POULTRY

TABLE OF CONTENTS

A. Action Requested 5

B. Statement of Grounds 7

I. EXECUTIVE SUMMARY 7

II. INTEREST OF THE PETITIONERS 17

III. INTRODUCTION 19

a. The Extensive Use of Antibiotics in Animal Agriculture Has Led to a Public Health Crisis 19

b. FDA Must Prevent the Extensive Use of Antibiotics in Animal Agriculture 22

IV. LEGAL STANDARD FOR APPROVAL OF ANIMAL ANTIBIOTICS AND FDA ACTION 23

a. FDA Has a Mandatory Duty to Withdraw Approval of Current Unsafe Uses of MIAs in Animals 23

1. FDA Has a Mandatory Duty to Withdraw Approval of Animal Drugs Not Shown to Be Safe for Human Health 23

2. The FFDCA Sets Forth a Clear Legal Standard for Determining Whether an Animal Drug is Safe 23

3. Current Uses of MIAs Are Unsafe Under the FFDCA 24

4. FDA Has Refused to Withdraw Unsafe Uses of MIAs, Opting Instead for a Program of Voluntary Compliance 27

5. FDA's Program of Voluntary Compliance Is Not a Lawful Substitute for Proceedings to Withdraw Approvals for Unsafe Uses of MIAs 29

b. FDA Has Multiple Means at Its Disposal to Reduce the Administrative Burdens Associated with Withdrawal Proceedings 30

V. PAST FDA ACTIONS ARE INADEQUATE TO REDUCE THE RISK OF HARM FROM THE ROUTINE USE OF ANTIBIOTICS IN ANIMAL AGRICULTURE TO SAFE LEVELS 32

a. FDA Has Long Recognized the Risk of Routine Animal Use of Antibiotics on Human Health, and Yet Has Never Taken Adequate Action. 32

1. From the Beginning, the Routine Use of Antibiotics in Animal Feed and Water Was Not for Animal Health and Was Recognized as Dangerous to Human Health 33

2. Decades ago, FDA Acknowledged that the Use of Antibiotics in Agriculture Is Unsafe. 36

3. In the Late 1990's FDA Began Its Unsuccessful Effort to Manage the Public Health Risks of Antibiotics in Agriculture Through Voluntary Industry Compliance. 38

4. In the Decades Since, FDA Has Backtracked on or Ignored Much of its Own Non-Binding Guidance. 40

b. FDA's Guidance and Policies Continue to Allow the Use of Antibiotics for Disease Prevention and for Long Durations. 43

c. Current Routine Use of Medically Important Antibiotics in Animals Remains Extremely High. 45

d. Data Suggests that Antibiotics in Agriculture Are Mostly Used for Prevention, Not Treatment. 46

VI. SCIENCE IS CLEAR THAT THE ROUTINE USE OF MEDICALLY IMPORTANT ANTIBIOTICS IN ANIMAL FEED OR WATER FOR PREVENTATIVE USES IS NOT SAFE BECAUSE FDA CANNOT ESTABLISH A REASONABLE CERTAINTY OF NO HARM 48

a. The Core Science of How Antibiotic Use Creates Antibiotic Resistance Is Beyond Dispute. 49

1. All Antibiotic Use Can Drive Resistance. 49

2. Since Antibiotic Resistance Is Gene-Based, It Can Move Very Swiftly and Far. 52

3. Use of Antibiotics for Disease Prevention in Animals Leads to the Development of Resistance. 54

b. Science is Clear That Routine Animal Antibiotic Use Significantly Harms Humans, Animals, and the Economy. 56

1. Antibiotics, Resistant Bacteria, and Antibiotic Resistance Genes Are Transferred from Livestock and Poultry to Humans and the Environment. 56

2. Genetic Studies Confirm that Resistant Bacteria Are Transmitted Between Food Producing Animals and People. 62

3. The Use of Antibiotics in Livestock and Poultry and the Prevalence of Resistant Bacteria in Humans, Animals, and Animal Products Are Correlated. 64

4. Antibiotic Resistance in Humans Causes Significant Health Harms. 65

5. Antibiotic Resistance Harms Animals and the Economy. 67

c. Routine Antibiotic Use Is Not Necessary for Raising Livestock and Poultry. 67

d. Studies Show that Sufficiently Reducing Antibiotic Uses in Livestock and Poultry Has Reduced the Prevalence of Resistance. 69

VII. SINCE THE SCIENCE IS CLEAR THAT LONGER ANTIBIOTIC USE INCREASES THE RISK OF ANTIBIOTIC RESISTANCE, FDA SHOULD SET STRICT DURATION LIMITS ON ANY ANIMAL USE 72

a. Longer Duration Uses Are Not Safe. 73

b. Rather than Regulating Antibiotics to Prevent Dangerous Long Duration Use in Livestock and Poultry, FDA is Watering Down its Guidance on Duration of Use. 75

VIII. CURRENT DATA COLLECTION EFFORTS ARE INADEQUATE AND FDA SHOULD COLLECT SPECIES- AND PURPOSE-SPECIFIC USE DATA 76

IX. FDA SHOULD SET ANIMAL-SECTOR-SPECIFIC REDCUTION TARGETS AS TOOLS FOR COMBATTING ANTIBIOTICS RESISTANCE 79

X. CONCLUSION 80

C. Environmental Impact 80

D. Certification 81

Appendix A: Challenged Indications

Appendix B: J.M. Gilbert, A Review of Studies Submitted to CVM Assessing the Effects of Sub-Therapeutic Use of Antimicrobial Drugs on the Salmonella Reservoir in Food Producing Animals (2001)

Appendix C: Index of Cited Journal Publications

Appendix D: Index of Other Cited Sources

Appendix E: Request for an Advisory Opinion

Citizen Petition

Date: June 16, 2026

The undersigned organizations, representing millions of Americans and consumer, public health and health care provider, environmental, animal welfare, farm and farmworker, and rural communities, submit this petition under sections 512(e) and 701(a) of the Federal Food, Drug, and Cosmetic Act (FFDCA), 21 U.S.C. §§ 360b(e), 371(a), and the citizen petition procedures at 21 C.F.R. § 10.25(a), to request the Commissioner of Food and Drugs to take administrative action to initiate and implement the withdrawal of approval for certain uses of medically important antibiotics (MIAs) protect public health from unsafe uses MIAs in food-producing animals.

A. Action Requested

Petitioners submit this request to the Food and Drug Administration (FDA) to find pursuant to 21 C.F.R. § 514.115(b)(3)(ii) that the use of MIAs[1] in the feed and water of food-producing animals for maintenance of growth,[2] for long durations,[3] or in the absence of diagnosed illness (i.e. for disease prevention or technical purposes),[4] is "not shown to be safe." In addition, we petition FDA to withdraw approval of these same uses.[5]

Petitioners seek FDA's withdrawal of approval for the indications identified specifically in Appendix A of the following drugs:

I. Antibiotics Administered in Feed

1. Chlortetracycline

[1] Generally, medically important antibiotics refers to drugs in the same antibiotic classes as those used in human, but for this petition, we consider drugs in classes listed as medically important in Table A of draft Guidance for Industry #152, including the antibiotic tiamulin. Draft GFI #152, at 32 tbl. A2. Appendix A of this petition lists the antibiotics that we identified as covered by this petition.

[2] FDA worked with the drug industry to withdraw approval of the use of MIAs for growth promotion in a process described in Guidance for Industry #213. FDA, *Guidance for Industry #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* (2013) (GFI #213), https://www.fda.gov/media/83488/download. In implementing this process, FDA allowed the continued use of MIAs for the "maintenance of weight gains" in the presence of a specific disease as indicated by their continued approval. *See, e.g.,* 21 C.F.R. § 558.140(e)(1)(i) (2025). We ask that these indications be included among the others for which we are seeking an opinion and withdrawal.

[3] Under FDA's Guidance for Industry #152, the administration of an antibiotic to a group of food producing animal for over 21 days is considered high extent of use. FDA, *Guidance for Industry #152: Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern* 23 tbl. 7 (2003) (Original GFI #152), https://www.regulations.gov/document/EPA-HQ-OPP-2016-0519-0015. This petition requests an opinion on the safety of MIAs following under high extent of use and to withdraw these approvals as unsafe.

[4] FDA defines disease prevention as "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." GFI #209, at 21 n.5. With respect to disease-prevention uses, this petition is not limited to animal drug applications that include the word "prevention" in their approved conditions of use, but covers all routine uses of medically important antibiotics in livestock that meet the definition of "disease prevention" just quoted. The prevention use indications are bolded in Appendix A and include indications for "reduction of incidence" of various conditions. There are also three cases where the indication states an antibiotic is to be used to control a disease, but the label instructions require that the antibiotic be used before clinical diagnosis of illness thus meeting this definition of disease prevention. *See* 21 C.F.R. § 558.612(e)(1)(i) (2025) (tiamulin limitations stating to "[f]eed continuously as sole ration on premises with a history of swine dysentery but where signs of disease have not yet occurred"); *id.* § 558.618(e)(1)(i) (2025) (tilmicosin limitations stating to "[f]eed continuously as the sole ration for 21-day period, beginning approximately 7 days before an anticipated disease outbreak"); *id.* § 558.635(e)(2)(i) (2025) (virginiamycin label stating an indication for use "on premises with a history of swine dysentery but where symptoms have not yet occurred"). Oxytetracycline is approved for "[f]or skeletal marking of finfish fry and fingerlings," *id.* § 529.1660(d)(2) (2025), which is a technical use not for medical purposes, so not based on diagnosis of illness. This petition asks for this use to be withdrawn as well as it is contrary to FDA's own judicious use principles that MIAs only be used for animal health reasons.

[5] Petitioners also request that while withdrawal proceedings are pending, FDA issue an advisory opinion pursuant to 21 C.F.R. § 10.85 that these uses are not shown to be safe. A separate request for an advisory opinion is therefore accompanies this document as Appendix E.

2. Chlortetracycline and sulfamethazine
3. Erythromycin
4. Hygromycin B
5. Lincomycin
6. Oxytetracycline
7. Oxytetracycline and neomycin
8. Sulfadimethoxine and ormetoprim
9. Sulfaquinoxaline
10. Tiamulin
11. Tilmicosin
12. Tylosin
13. Tylosin and sulfamethazine
14. Virginiamycin

II. Antibiotics Administered in Water

1. Chlortetracycline and sulfamethazine
2. Oxytetracycline and carbomycin
3. Sulfamethazine
4. Sulfaquinoxaline
5. Oxytetracycline

Appendix A lists the specific indications, along with information on durations for the specific uses this petition is challenging.

Petitioners have not included in this petition the many animal drug combinations of MIAs with non-medically important antibiotics that also include these specified antibiotic indications. However, Petitioners are asking for the withdrawal of these combinations as well because feeding a non-medically important drug along with an unsafe MIA is still unsafe.

In addition, the Petitioners request that FDA take additional steps to begin collecting, summarizing, and reporting on antibiotics in feed distributed to food-producing animal raising facilities along with associated Veterinary Feed Directives (VFDs),[6] and to set public-health-based sector-specific targets for the reduction of antibiotic use in food animal production. These additional steps are required to monitor and measure the impacts of these and other efforts to ensure the safety of antibiotic drugs used in food animals.

[6] Veterinary Feed Directive drugs are drugs administered in feed that require a veterinarian's order before use. The Veterinary Feed Directive or VFD is the order written by a veterinarian authorizing use and includes information such as species and production class of animal, level of drug in feed, and the indication (reason) for use of the drug.

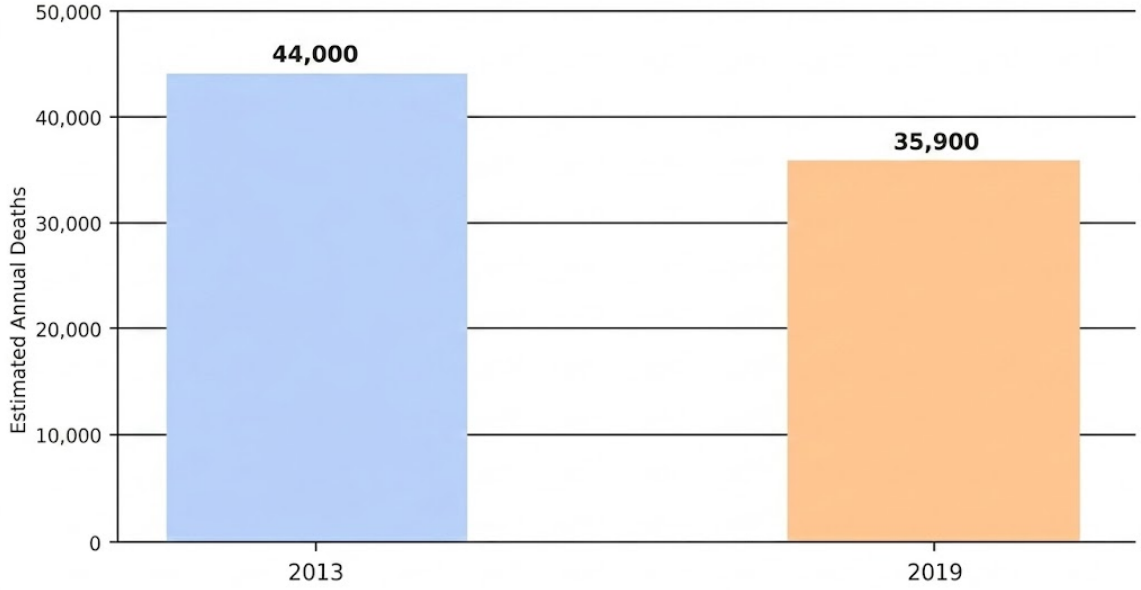
B. Statement of Grounds

I. EXECUTIVE SUMMARY

The Routine Use of Antibiotics in Animal Feed and Water Poses a Major Public Health Threat

The routine use of antibiotics in animal feed and water for disease prevention rather than treatment or control of diagnosed bacterial diseases threatens the effectiveness of medically important antibiotics. These antibiotics are essential for surgery, chemotherapy, organ transplantation, and the care of premature human infants, not to mention the treatment of many common bacterial diseases. This overuse of antibiotics leads to the creation of antibiotic-resistant bacteria that then sicken and kill people and animals, risking the health and welfare of all Americans and people around the world. Indeed, antibiotic-resistant bacteria are already responsible for about 35,000 deaths and over two million illnesses every year in the United States alone. All of this is well known and undisputed.

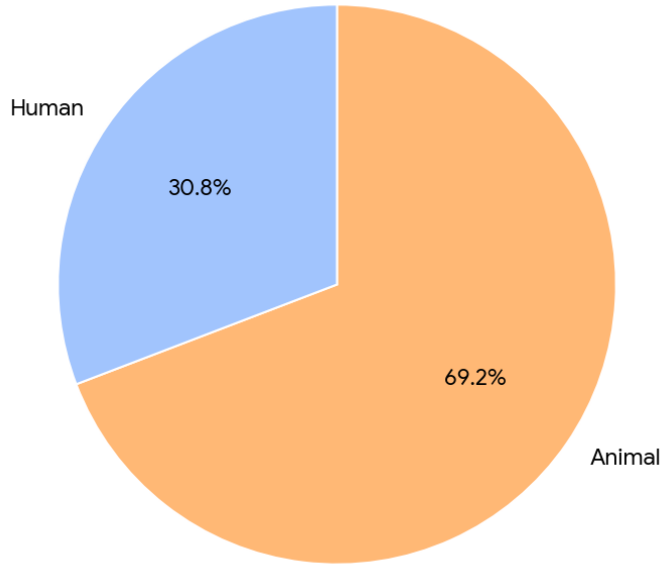
Figure 1. Estimated U.S. Deaths from Antibiotic-Resistant Infections[7]



[7] Centers for Disease Control and Prevention, *Antibiotic Resistance Threats in the United States 2019*, at 3, 6 (2019), https://www.cdc.gov/antimicrobial-resistance/data-research/threats/index.html (updating the estimated number of deaths caused by antibiotic resistance in 2013 to be nearly 44,000 deaths and estimating 35,900 deaths caused by antibiotic resistance in 2019). The 2019 figure of 35,900 AR deaths reflects an 18% reduction resulting from dedicated prevention and infection control efforts between 2013 and 2019.

While both animal agricultural use and human health use contribute to antibiotic resistance, there is far less justification for any use of antibiotics other than control or treatment of disease. Despite that widely acknowledged fact, the significant majority of antibiotics sold in the U.S. are used not to treat sick people or even sick animals. Rather, most antibiotics are given to entire herds of livestock or flocks of poultry via feed or water, often for extended periods, for disease prevention. This long-term low-level dosing creates the ideal conditions to maximize selective pressure for, and expand reservoirs of, resistant bacteria and resistance genes. This also is well known and undisputed. It is time for FDA to end this unsafe practice.

Figure 2. Estimated U.S. Antibiotic Sales for Use in Food-Producing Animals vs. Use in Human Medicine (2020)[8]



A Robust Body of Science Demonstrates that Current Uses of Antibiotics in Agriculture Are Unsafe

There is a broad consensus among public health authorities, including FDA and Centers for Disease Control and Prevention (CDC) that the use of antibiotics in livestock production significantly contributes to the development and spread of antibiotic resistance transmissible to people and animals. The mechanisms and harms are clear:

1. Antibiotic exposure selects for resistant bacteria by killing off non-resistant bacteria and leaving a population of resistant bacteria;
2. Prolonged, low-dose group administration accelerates selection, co-selection on mobile genetic elements, and horizontal gene transfer by creating ideal conditions for resistant bacteria to spread widely;

[8] David Wallinga, *Antibiotic Use Remains Far Too Intensive in U.S. Livestock*, Nat. Res. Def. Council (Sep. 11, 2023), https://www.nrdc.org/bio/david-wallinga-md/antibiotic-use-remains-far-too-intensive-us-livestock. Human sales data was obtained by IQVIA and provided by One Health Trust. FDA does not track antibiotic use, so researchers use sales data as the best available indication of use.

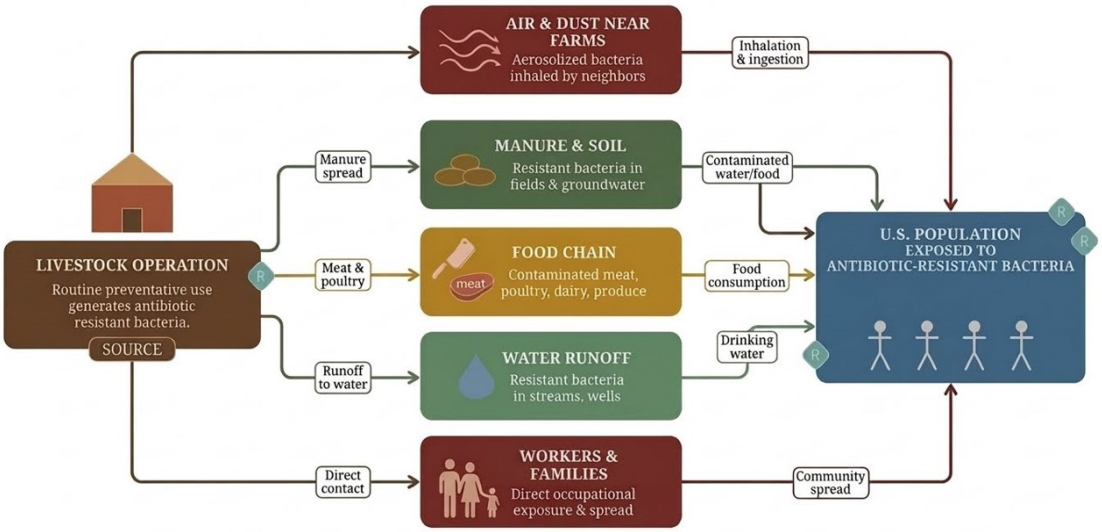
3. Resistant pathogens—including non-typhoidal *Salmonella* and *Campylobacter*—lead to increased hospitalization and more difficult-to-treat infections because standard treatments are ineffective; and
4. Opportunistic (i.e., normally harmless) pathogens such as *Escherichia coli*, *Staphylococcus aureus*, and *Enterococcus* can acquire resistance in agricultural settings and then also contribute to human illness when transmitted from those settings to vulnerable human hosts.

Dozens of expert studies confirm this, demonstrating, for example, that antibiotic use in animal agriculture results in the spread of resistant bacteria to humans by:

- Showing that bacteria exchange resistance genes not only among the same bacteria but between different bacterial species.
- Comparing genetic similarity between bacteria in animals and humans;
- Comparing high animal agriculture regions to low animal agriculture regions;
- Comparing conventional agriculture that uses antibiotics with organic agriculture that does not;
- Analyzing samples of water, air, and dust near animal factories, finding antibiotic-resistant bacteria;
- Examining the bacteria found in farm workers and neighbors of animal operations;
- Analyzing retail meat and poultry (even that deemed "antibiotic free").

Numerous studies have also shown that multiple pathways connect on-farm use of antibiotics, and thus on-farm selection of antibiotic resistance, with human exposure. Humans are exposed through contamination of meat and poultry at slaughter and retail; consumption of meat and poultry containing antibiotic resistant bacteria; direct occupational exposure; movement of air and dust from facilities; runoff and leaching of manure-borne bacteria and resistance genes into soil and water; and transfer of resistance determinants across bacterial species.

Figure 3. Pathways by Which Antibiotic-Resistant Bacteria Travel from Food-Producing Animals to Humans[9]



This science is not new or hidden. Indeed, FDA[10] and the CDC[11] have known for many decades that the misuse and overuse of antibiotics can contribute to antibiotic resistance that transfers to humans and thus poses a human health risk. Reflecting this knowledge, in 1977, FDA proposed to take action to end the misuse of antibiotics, but heavy lobbying pressure from the pharmaceutical and livestock industries got Congress to intervene and prevented FDA from proceeding.

More recently, Martin Makary, who recently resigned as FDA Commissioner, urged physicians to "draw attention to the association between routine antibiotic use in animals and the declining efficacy of antibiotics in treating human infections," acknowledged "the health and economic consequences of antibiotic misuse in animal production," and explained that "we have created this massive public health problem that affects children" and others who are vulnerable.[12]

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[9] CDC, *Antibiotic Resistance Threats in the United States 2019*, at vii (2019), https://www.cdc.gov/antimicrobial-resistance/data-research/threats/index.html.

[10] *Antimicrobial Resistance*, FDA, https://www.fda.gov/animal-veterinary/safety-health/antimicrobial-resistance (last updated Dec. 5, 2025); *Know When and How to Use Antibiotics, and When to Skip Them*, FDA, https://www.fda.gov/consumers/consumer-updates/know-when-and-how-use-antibiotics-and-when-skip-them (last updated Nov. 18, 2024).

[11] *Antimicrobial Resistance: Causes and How It* Spreads, CDC (Sep. 25, 2025), https://www.cdc.gov/antimicrobial-resistance/causes/index.html; *U.S. Actions & Events to Combat Antimicrobial Resistance*, CDC (Dec. 19, 2024), https://www.cdc.gov/antimicrobial-resistance/programs/AR-actions-events.html.

[12] Curt Chaffin, The Good Food Institute, *The Same Entities that Helped Create Antibiotics Are Advancing Alternative Proteins*, Alt Protein Planet (Apr. 18, 2025), https://thegoodfoodinstitute.substack.com/p/the-same-entities-that-helped-create ("Dr. Makary has dedicated significant attention to the role agriculture plays in antimicrobial resistance."); Martin A. Makary, Katerina Kaczmarski & Keeve Nachman, *A Call for Doctors to Recommend Antibiotic-Free Foods: Agricultural Antibiotics and the Public Health Crisis of Antimicrobial Resistance*, 71 J. Antibiotics 685 (2018); Tedx Talks, *The Next Pandemic | Marty Makary | TedxPearlStreet*, at 13:26 (YouTube, Oct. 1, 2020), https://www.youtube.com/watch?v=8rp3dSMaz4Q ("Antibiotics in livestock is a major driver of antibiotic resistance. . . . 70 to 80 percent of all the antibiotics produced are used in animals. Why? For no good reason. It's so the animals can be crowded and used in factory farming techniques and sometimes cruel

Makary added that, although it was believed that the use of antibiotics in food animals "could prevent disease before it happens . . . we've learned [] that the routine use of antibiotics in agriculture has some disastrous implications for public health in humans."[13]

Citizen groups have also sounded the alarm. For example, an Environmental Working Group (EWG) analysis of more than 47,000 lab tests of bacteria found on supermarket meat detected antibiotic resistant bacteria on the majority of turkey, pork chop, and ground beef samples tested.[14]

There is also growing public awareness of the dangers posed by using antibiotics in animal feed and water. One national poll found that the vast majority of Americans believe antibiotic use on dairy farms threatens human health, and that most would be willing to pay more for milk from cows that were not given antibiotics.[15] In another national poll, two-thirds of Americans said that antibiotic-free labels were important to them when purchasing meat, and 75% said that they would be willing to pay more for meat that was antibiotic-free.[16]

And here, petitioners, representing millions of people threatened or already harmed by unsafe use of antibiotics are demanding that FDA finally act. Petitioners include health care workers, threatened when patients have antibiotic resistant infections; animal agriculture workers who are especially threatened by antibiotic resistant bacteria, which is found in higher concentrations at and near animal facilities; people downwind or downstream of animal production facilities, also

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conditions ."); *A Call for Doctors to Lead the Charge for Antibiotic-Free Foods*, Johns Hopkins Medicine (June 1, 2018), https://www.hopkinsmedicine.org/news/newsroom/news-releases/2018/06/a-call-for-doctors-to-lead-the-charge-for-antibiotic-free-foods. Makary also stated that "about 20 percent, now, of all the antimicrobial-resistant infections that we see in the hospital probably originated from agriculture and from the overuse of antibiotics in agriculture." In fact, around 20% of resistant infections are associated with *Campylobacter* and non-typhoidal *Salmonella* alone. *See* CDC, *Antibiotic Resistance Threats in the United States 2019*, at 17 (2019), https://www.cdc.gov/antimicrobial-resistance/data-research/threats/index.html. The figure Makary cited does not include the many other resistant pathogens originating in the use of antibiotics in agriculture. *See*, *e.g.*, Maliha Aziz et al., *Zoonotic Escherichia coli and Urinary Tract Infections in Southern California*, 16 Clinical Microbiology (2025); Vanessa Silva et al., *Staphylococcus aureus and MRSA in Livestock: Antimicrobial Resistance and Genetic Lineages*, 11 Microorganisms (2023). In other words, it is likely that significantly more than 20% of anti-microbial resistant infections in hospitals originated from the overuse of antibiotics in agriculture.

[13] PIRGvideos, *Dr. Marty Makary Addresses Antibiotic Resistance – 4 Minutes*, at 1:15 (YouTube, July 11, 2018), https://www.youtube.com/watch?v=VdygxfL9iFc; *This Infection Is Resistant to Everything We Have*, PIRG (Oct. 4, 2018), https://pirg.org/articles/this-infection-is-resistant-to-everything-we-have/.

[14] *See* Aurora Meadows, *Supermarket Meat Still Superbugged, Federal Data Show*, Env't Working Grp. (June 28, 2018), https://www.ewg.org/research/superbugs; *see also* Zen Honeycutt, *Contraceptive and Harmful Antibiotics Found in Top Ten Fast Food Samples*, Moms Across Am. (Oct. 9, 2023), https://www.momsacrossamerica.com/blog/harmful_antibiotics_and_a_contraceptive_found_in_top_ten_fast_food_samples (testing foods from the top U.S. restaurant chains, finding antibiotic residues in food from seven out of the top ten chains, and concluding, "[o]ne thing is certain: long-term exposure to antibiotics . . . in foods can cause serious health problems like antibiotic resistance.").

[15] M. Wemette et al., *Public Perceptions of Antibiotic Use on Dairy Farms in the United States*, 104 J. Dairy Sci. 2807 (2021).

[16] John Zogby, *Antibiotic-Free Labels Are Important to Two-Thirds of Americans when Buying Meat – and Data to Back-Up Claims Is Paramount, a New Poll Shows*, Forbes (Feb. 11, 2021), https://www.forbes.com/sites/johnzogby/2021/02/11/antibiotic-free-labels-are-important-to-two-thirds-of-americans-when-buying-meat---and-data-to-back-up-claims-is-paramount-a-new-poll-shows/.

at increased risk; and just average Americans who are at risk from antibiotic resistant bacteria that are all around us.

Antibiotic resistance resulting from antibiotic use in food-producing animals is particularly pernicious because individuals can do little to protect themselves from it. Antibiotic-resistant bacteria are in the air we breathe, the water we drink, and the food we eat, even if we only buy meat and poultry raised without antibiotics or live far from farming operations. The only way Americans will be safe is for FDA to comply with its legal obligation to end the routine use of antibiotics in animal feed and water other than for treating or controlling diagnosed disease.

The Routine Preventive Use of Antibiotics in Animal Feed and Water Is Not Necessary for Raising Livestock and Poultry

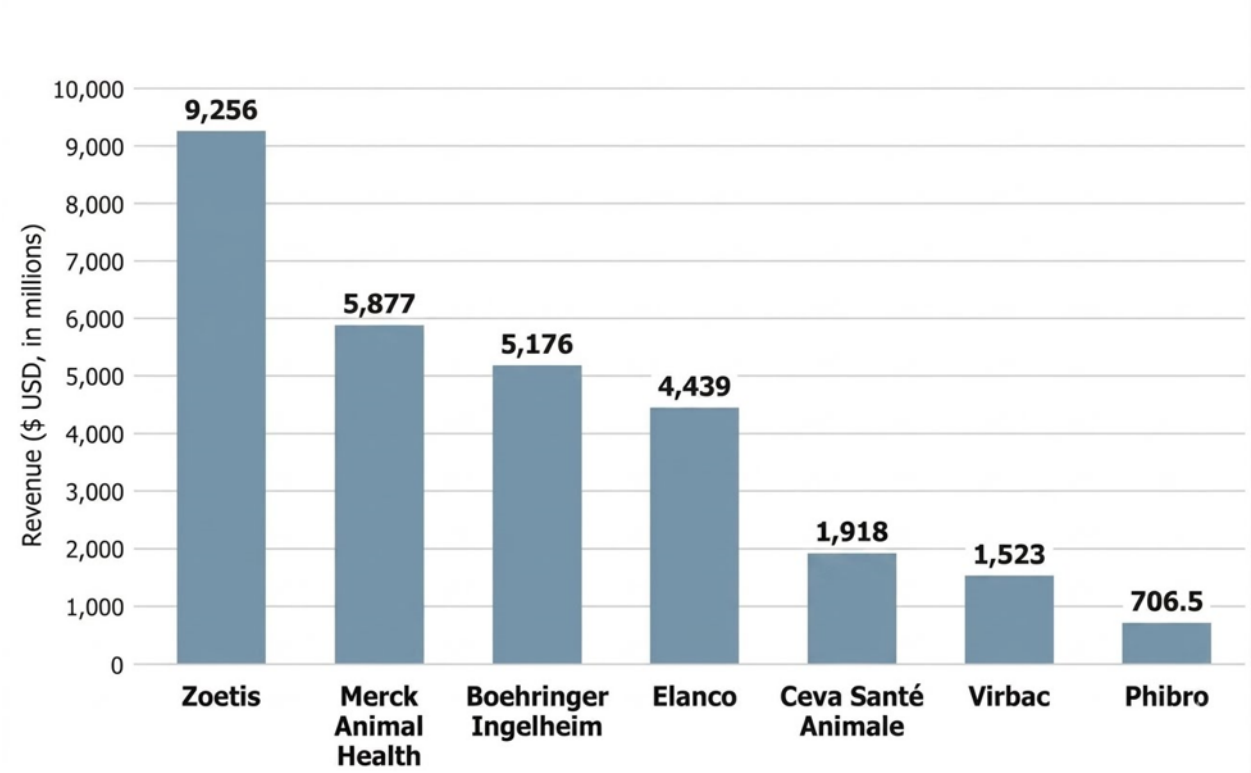
The animal agriculture and pharmaceutical industries have pressed hard to stop FDA from withdrawing approval for the use of antibiotics in disease prevention and for long durations. However, the routine use of antibiotics in agriculture for disease prevention and for long durations is not only dangerous, but it is also entirely unnecessary.

Indeed, the routine use of antibiotics in food animals did not start to solve a pressing agricultural need. Rather, the practice started because the pharmaceutical industry hoped to establish a larger market for antibiotics. The pharmaceutical industry sought long-term, rather than episodic, uses and heavily promoted the use of antibiotics for growth promotion and to enable less costly animal maintenance practices. Since then, the industry has continued to extensively market this long-term use.

According to industry analysis, the U.S. market for production animal medicines is about $8 billion per year, and the U.S. animal drug industry is growing at over 7.5%-per year.[17] The global market for farm animal drugs is almost three times that.[18] One analysis notes that "growth [in the U.S. veterinary medicine market] is being fueled by the widespread use of medications in livestock, the increasing focus on preventing and controlling diseases, and more intensive farming practices."[19]

[17] *U.S. Veterinary Medicine Market (2025 - 2033)*, Grand View Rsch., https://www.grandviewresearch.com/industry-analysis/us-veterinary-medicine-market-report (last updated Sep. 2025) (including other medicines, diagnostics and non-drug additives, in addition to antibiotics).
[18] *Farm Animal Drug Market: Global Industry Analysis 2015 - 2024 and Opportunity Assessment 2025 – 2035*, Future Mkt. Insights Inc., https://www.futuremarketinsights.com/reports/farm-animal-drugs-market (last updated Oct. 7, 2025).
[19] *U.S. Veterinary Medicine Market (2025 - 2033)*, Grand View Rsch., https://www.grandviewresearch.com/industry-analysis/us-veterinary-medicine-market-report (last updated Sep. 2025).

Figure 4. Estimated Global Sales of Seven Major Animal Health Companies (2024, Net Manufacturer Revenue for Animal Health)[20]



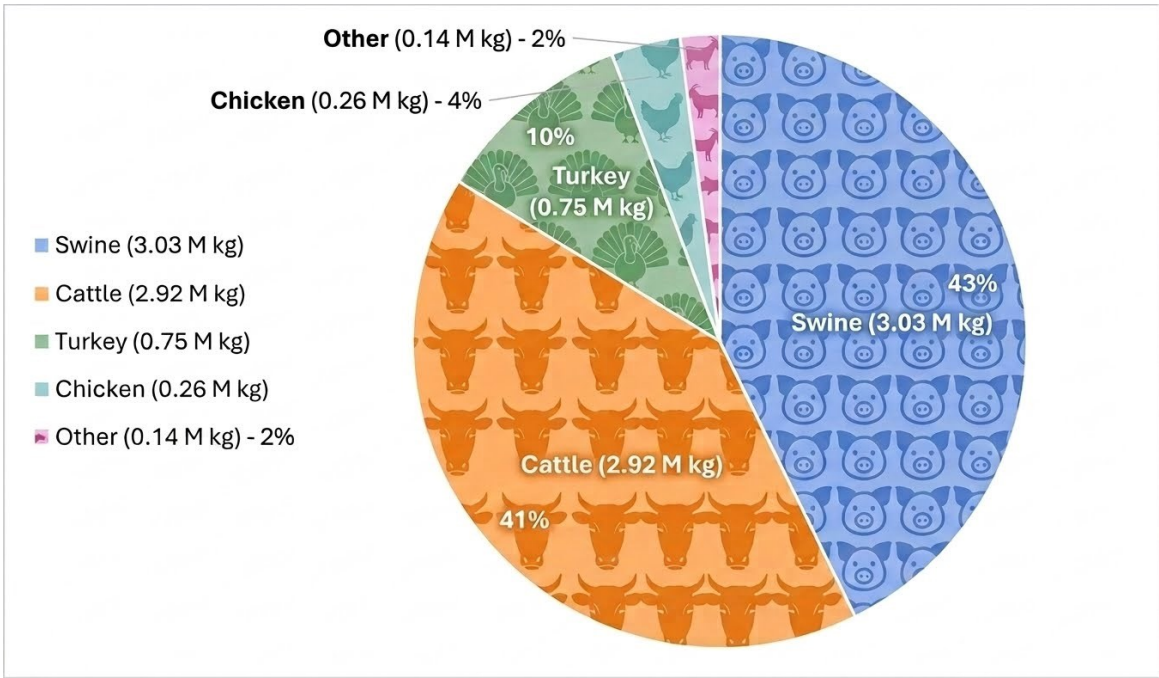
Despite claims as to the need for disease prevention use, improved animal husbandry can largely eliminate this need. This is made clear, first and foremost, by the work of thousands of farmers who raise livestock and poultry with very infrequent use of antibiotics (such as if the antibiotics

[20] All revenue figures are for the calendar year ended December 31, 2024, except Phibro Animal Health, which reports on a fiscal year ending June 30. All figures represent manufacturer net revenue and are not directly comparable to end-market or retail-level market size estimates. Currency conversions from EUR to USD use approximate 2024 average exchange rates (~1.09 USD/EUR). *See* Zoetis, *2024 Annual Report* (2025), https://s203.q4cdn.com/620628704/files/doc_downloads/2025/Zoetis-2024-Annual-Report.pdf; *Merck Announces Fourth-Quarter and Full-Year 2024 Financial Results*, Merck (Feb. 4, 2025), https://www.merck.com/news/merck-announces-fourth-quarter-and-full-year-2024-financial-results/; Boehringer Ingelheim, *2024 Highlights: Think Beyond* (2025), https://www.boehringer-ingelheim.com/annualreport/2024/files/downloads-and-archive/highlights-2024/BOE_Highlights_2024_EN.pdf (reporting 4,749 million euros in total revenue for animal health in 2024); Elanco, *2024 Annual Report* (2025), https://assets.elanco.com/63faca97-0277-00f3-7b39-47b486080a51/99e38b60-2f28-4a0f-9254-8e23b06e3f9f/AR_601875.pdf; Ceva Santé Animale, *Non-Financial Performance Statement 2024* (2025), https://www.ceva.com/wp-content/uploads/2025/10/EN-CEVA_DPEF_24_WEB.pdf (reporting 1.76 billion euros in total revenue for animal health in 2024); Virbac, *Annual Report 2024* (2025), https://corporate.virbac.com/files/live/sites/virbac-corporate/files/contributed/RA2024/PDF/Annual_report_Virbac_2024.pdf (reporting 1,397 million euros in total revenue for animal health in 2024); *Phibro Animal Health Corporation Reports Fourth Quarter and Fiscal Year Results, Provides Financial Guidance*, Phibro Animal Health Corp. (Aug. 28, 2024), https://investors.pahc.com/press-releases/press-release-details/2024/Phibro-Animal-Health-Corporation-Reports-Fourth-Quarter-and-Fiscal-Year-Results-Provides-Financial-Guidance/default.aspx. Phibro Animal Health acquired Zoetis's medicated feed additive portfolio and certain water soluble products and related assets in 2024, but Zoetis continues to sell other veterinary antibiotic products.

are needed to treat illness) or not at all. Indeed, the chicken industry uses ten times less antibiotics per pound of meat produced than the cattle and swine industries.

While the beef industry as a whole uses much more antibiotics than the chicken industry, a recent United States Department of Agriculture (USDA) study found that over half of all feedlots gave no antibiotics in feed (the primary delivery mechanism), including over 30% of the largest feedlots.[21] Similarly, USDA data show that more than 20% of sites raising nursery pigs in traditional systems reported no antibiotic use in feed,[22] and over 30% reported no use in water.[23] So, even in the sectors with heavy use many producers have found ways to use much lower levels of antibiotics.

Figure 5. U.S. Medically Important Antibiotic Sales by Animal Species: Distribution (2024)[24]



In addition, extensive evidence from multiple European countries indicates that it is possible to profitably raise pigs and cattle with much lower levels of antibiotic use than what is used on average U.S. farms and feedlots.[25]

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[21] USDA, *Management Practices on U.S. Feedlots, 2021*, at 54 tbl. G.5.a (2024), https://www.aphis.usda.gov/sites/default/files/feedlot-health-2021-mgmt-practice-dr1.pdf.
[22] USDA, *Swine Part II: NAHMS 2021 – Reference of Management Practices on Large-Enterprise Swine Operations in the United States* tbl. C.5.f. (2021), https://www.aphis.usda.gov/livestock-poultry-disease/nahms/swine/swine-2021-part-ii-reference-management-practices-large.
[23] *Id.* at tbl. C.5.c.
[24] FDA, *2024 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals* tbl. 4a (2025), https://www.fda.gov/animal-veterinary/antimicrobial-resistance/2024-summary-report-antimicrobials-sold-or-distributed-use-food-producing-animals.
[25] David Wallinga & Avinash Kar, *Very High Livestock Antibiotic Use Undercuts Effective Drugs: Beef and Pork Industries Must Do Better to Help Curb Antibiotic Resistance*, Nat. Res. Def. Council (Dec. 12, 2019), https://www.nrdc.org/bio/david-wallinga-md/very-high-livestock-antibiotic-use-undercuts-effective-drugs; *see also*

This evidence, coupled with the growing market success of organic and "raised without antibiotics" meat and poultry, makes clear that the routine use of antibiotics in feed and water for disease prevention is simply unnecessary for successful production or disease prevention. And in addition to being economically feasible, substantial reductions in antibiotic use would result in measurable benefits to public health. As detailed later in this Petition, study after study has shown that by sufficiently reducing antibiotic use in livestock, FDA would drive significant corresponding reduction in antibiotic resistance.

The Law Is Clear that FDA Must Take Sufficient Action to End Unsafe Uses of Antibiotics

Under the FFDCA, FDA must initiate a process to withdraw approval of any animal drug use that is "not shown to be safe" for human or animal health.[26] In other words, if a drug may pose "harm to human health," FDA must find it to be unsafe.[27] FDA must look to the probable consumption of the drug, the cumulative impact of the drug and related substances, a margin of safety, and the real-world use conditions and will – indeed it must – find a drug use unsafe unless that use poses a "reasonable certainty of no harm."[28]

Despite the overwhelming evidence that the routine use of antibiotics for disease prevention and for long durations harms human health, FDA, perhaps cowed by the pharmaceutical and animal agriculture industries' lobbies, has never tried to take sufficient action stop this misuse. To the contrary, FDA continues to allow antibiotics to be used in food producing animals not diagnosed with any disease and for long durations. Moreover, in addition to licensing these misuses of antibiotics, FDA has failed even to collect and disseminate data germane to the misuse of antibiotics, clouding the public's view into the extent of the problem. And over the decades industry marketing campaigns have driven massive sales of antibiotics for use in animal agriculture by both encouraging overuse and by downplaying risks to public health.

Consumer, health, and environmental groups sued FDA for this inaction in 2012. After the groups won in district court, the appellate court ruled for FDA, upholding as rational FDA's decision to encourage voluntary compliance with medically appropriate animal antibiotic use rather than revoke approvals of inappropriate uses.[29] FDA made much of the fact that, apparently

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Marcel van Asseldonk et al., *Antibiotics Use Versus Profitability on Sow Farms in the Netherlands*, 178 Preventive Veterinary Med. (2020); L. Collineau et al., *Herd-Specific Interventions to Reduce Antimicrobial Usage in Pig Production Without Jeopardising Technical and Economic Performance*, 144 Preventive Veterinary Med. 167 (2017); M. Postma et al., *Reducing Antimicrobial Usage in Pig Production Without Jeopardizing Production Parameters*, 64 Zoonoses & Pub. Health 63 (2017); Cristina Rojo-Gimeno et al., *Farm-Economic Analysis of Reducing Antimicrobial Use Whilst Adopting Improved Management Strategies on Farrow-to-Finish Pig Farms*, 129 Preventive Veterinary Med. 74 (2016); David Wallinga, Nat. Res. Def. Council (NRDC), *U.S. Livestock Industries Persist in High-Intensity Antibiotic Use: Curbing Overuse Is Critical to Slow the Spread of Antibiotic Resistance* (2022), https://www.nrdc.org/sites/default/files/us-livestock-industries-persist-high-intensity-antibiotic-use-ib.pdf.

[26] *See* 21 C.F.R. § 514.115(b) (2025).

[27] *See* FDA, *Guidance for Industry #209: The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals* 18 (2012) (GFI #209), https://www.fda.gov/media/79140/download (noting that the standard applies even "after approval" of a drug); FDA, *Final Decision of the Commissioner: Withdrawal of Approval of the New Animal Drug Application for Enrofloxacin in Poultry* 93–94 (July 27, 2005), https://www.regulations.gov/document/FDA-2000-N-0109-0137.

[28] *Id.*; 21 U.S.C. § 360b(d)(2).

[29] *See NRDC v. FDA*, 760 F.3d 151, 175 (2d Cir. 2014).

in response to the lawsuit, the agency limited the use of antibiotics for growth promotion. Unfortunately, FDA still allowed the largely overlapping use in animals without diagnosed disease for disease prevention. Moreover, FDA continued to issue only "nonbinding recommendations" to drug manufacturers, rather than enforceable mandates.[30]

Advocates petitioned FDA to act to stop the misuse of antibiotics in animal agriculture again in 2016 and FDA denied that petition, again relying on the measures it had pushed the industry to voluntarily adopt instead. While these measures briefly reduced animal agriculture antibiotic sales (a proxy for use since – again to due industry lobbying – FDA does not have the authority to mandate reporting of animal agriculture antibiotic use), recent evidence shows sales of antibiotics for use in agriculture are now again dangerously increasing. Moreover, a substantial—and still growing—body of scientific evidence since that time demonstrate that the use of antibiotics for disease prevention contributes to antibiotic resistance that is transferred to humans at unsafe levels. Accordingly, this Petition is supported by ample new scientific evidence including 89 studies since June 10, 2021, when FDA issued Guidance for Industry (GFI) #263; and another 84 since December 12, 2013, when FDA adopted GFI #213. As explained further below, these two dates are notable because they are milestones in the implementation of FDA's unsuccessful effort to deal with the problem of antibiotic overuse in animal agriculture through the adoption of non-binding guidance for industry and the promotion of voluntary industry compliance.

Thus, the 2014 court's finding that FDA's reliance on partial, voluntary measures is sufficient to meet the agency's mandate under the FFDCA is simply out of date. Courts are clear that "[d]ecisions which are not arbitrary and capricious in the light of existing knowledge may become so by the dint of scientific advances."[31] That is the case here. The horrifying reality is that antibiotic-resistant disease now kills 35,000 Americans every year, and sickens over 2 million others – it should be inconceivable that FDA still asserts that this is safe.

Given the many pathways – food, air, water, or contact – that link antibiotic use in animal production to human exposure to antibiotic resistant bacteria and resistance genes, individuals cannot insulate themselves from these antibiotic-resistant bacteria. For example, consumers avoiding the consumption of certain animal products may still be exposed by air, water, or other food consumers. However, policy interventions to reduce antibiotic use can help protect the public from resistant bacteria. Indeed, multiple studies show that restricting certain antibiotic uses in food animals is followed by measurable declines in resistance—thus confirming that policy interventions to reduce system use and exposure work.[32]

[30] *See, e.g.,* GFI #213.
[31] *Ala. Power Co. v. Costle*, 636 F.2d 323, 388 n.116 (D.C. Cir. 1979) (quoting *Texas v. EPA*, 499 F.2d 289, 301 n.16 (5th Cir. 1974)).
[32] *See* infra Section B.VI.

FDA Must Take the Following Actions to Ensure that the Use of Antibiotics in Animal Agriculture is Safe

Petitioners request that FDA take the following actions to ensure that the use of antibiotics in animal agriculture is safe as required by Congress.

- FDA must find that the current routine use of antibiotics in animal feed and water when not associated with diagnosed illness does not meet the mandated standard of presenting a "reasonable certainty of no harm."
- FDA must withdraw approval of antibiotics administered in feed or water when not associated with diagnosed illness—including "disease prevention" or "technical purposes"— and for the non-medical purpose of "maintenance of growth."
- FDA should use the regulatory tools at its disposal to expedite and streamline these withdrawal proceedings.
- FDA should prohibit labeled durations that constitute high extent of use – group administration beyond 21 days – consistent with FDA's risk-management framework in GFI #152.[33]
- FDA should begin systematic collection and reporting of species- and sector-specific antibiotic use data by leveraging existing feed-distribution records and Veterinary Feed Directives (VFDs).
- FDA should set public-health-based reduction targets for antibiotic use by livestock sector (e.g., poultry, swine, dairy cattle, beef cattle) to drive to drive greater transparency and measurable improvements in antibiotic stewardship" in animal agriculture, as HHS is already pursuing for antibiotic use in human medicine.

II. INTEREST OF THE PETITIONERS

The Petitioners are 65 organizations harmed by and concerned about the overuse of antibiotics in animal agriculture. Petitioners, their members, and their supporters are harmed by infections from antibiotic resistant bacteria, and other deleterious agricultural practices facilitated by the overuse of antibiotics in agricultural settings.

Consumer Advocacy Petitioners, such as the Center for Food Safety, Consumer Reports, Public Citizen, the National Consumer League, and Moms Across America, represent millions of consumers who rely on FDA to ensure that food on grocery shelves across the nation is produced in a manner that guarantees the public's safety. Consumer advocacy organizations have signed on to the Petition due to the harms caused to their members by the overuse of antibiotics in animal agriculture, which increases consumers' risk of exposure to antibiotic resistant bacteria.

Healthcare Petitioners, like Alliance of Nurses for Healthy Environments, the Lymphoma Foundation of America, and Healthcare Without Harm, represent the interests of patients suffering from antibiotic resistant bacterial infections and their healthcare providers. More active regulation of antibiotic use in animal agriculture by FDA would, in addition to reducing patient

[33] FDA, *Draft Guidance for Industry #152: Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern* 20 tbl. 7 (2023) (Draft GFI #152), https://www.fda.gov/media/69949/download.

illness and mortality, reduce doctors, nurses, and other healthcare workers' risk of exposure to antibiotic resistant bacteria. In short, the supporters and members of these Petitioners are on the frontlines of the crisis of antibiotic resistant infections resulting from the overuse antibiotics in animal agriculture.

Other frontline Petitioners, such as the Farmworker Association of Florida and the California Rural Legal Assistance Foundation, represent agricultural workers who may work directly with livestock and poultry subject to antibiotic overuse. These workers are particularly susceptible to harm from antibiotic resistant bacteria because of the nature of their work. Farmworkers in facilities that overuse antibiotics may be directly exposed to reservoirs of antibiotic resistant bacteria. In many cases, these workers are also vulnerable because of their limited access to healthcare and PPE, as well as their unsafe workplace conditions.

Petitioners, like Socially Responsible Agriculture Project, represent rural communities that similarly are especially vulnerable to antibiotic overuse in animal agriculture by dint of proximity to agricultural facilities, like CAFOs.

Organic and family farmers who are represented by Petitioners, like Northeast Organic Farmers Association of New York, American Regeneration, and Farm Aid, may also be harmed by their proximity to agricultural facilities that overuse antibiotics, and by their need to compete with industrial agricultural businesses that overuse of antibiotics instead of practicing safe and hygienic animal husbandry.

Several Petitioners are environmental organizations, like the Center for Biological Diversity and the Environmental Working Group. Environmental organizations have an interest in this Petition both because of the public health crisis associated with the spread of resistant bacteria and because the overuse of antibiotics facilitates unsanitary and environmentally harmful farming practices that have negative impacts on air, soil, and water. Some environmental Petitioners, like Hudson Riverkeeper, the Delaware Riverkeeper Network, and the Buffalo River Watershed Alliance are especially concerned by the impacts of industrial agricultural facilities, which use antibiotics, on their members' water sources. For example, Hudson Riverkeeper advocates for protection of a watershed containing approximately 60 regulated CAFOs presumed to use antibiotics and has measured antibiotic resistant bacteria in the Hudson River.

Animal Welfare Petitioners, like the Animal Legal Defense Fund, Mercy for Animals, and FOUR PAWS, recognize that pairing reductions in the use of agricultural antibiotics with improved animal welfare practices is integral to safeguarding human, animal, and environmental health.

Finally, Petitioners, like Antibiotic Resistance Action Center at George Washington University and Food Animal Concerns Trust, have specialized expertise on the development of antibiotic-resistant bacteria in agricultural settings. These Petitioners have corresponding specialized, scientifically-informed insight into effective policies that FDA could adopt to reduce the spread of such resistant bacteria.

FDA's grant of the Petition would meaningfully redress many of the harms suffered by the Petitioners and their members and supporters. By granting the Petition FDA would commit to taking concrete regulatory action to reduce the use of antibiotics in animal agriculture, and

thereby slow the proliferation of antibiotic resistant bacteria. These regulatory actions would reduce the risk that consumers, healthcare workers, rural communities, and farmers will fall ill with antibiotic resistant infections. The actions would also help to promote more environmentally sustainable and humane agricultural practices across the country, which would benefit the Petitioners as well as millions of other Americans.

III. INTRODUCTION

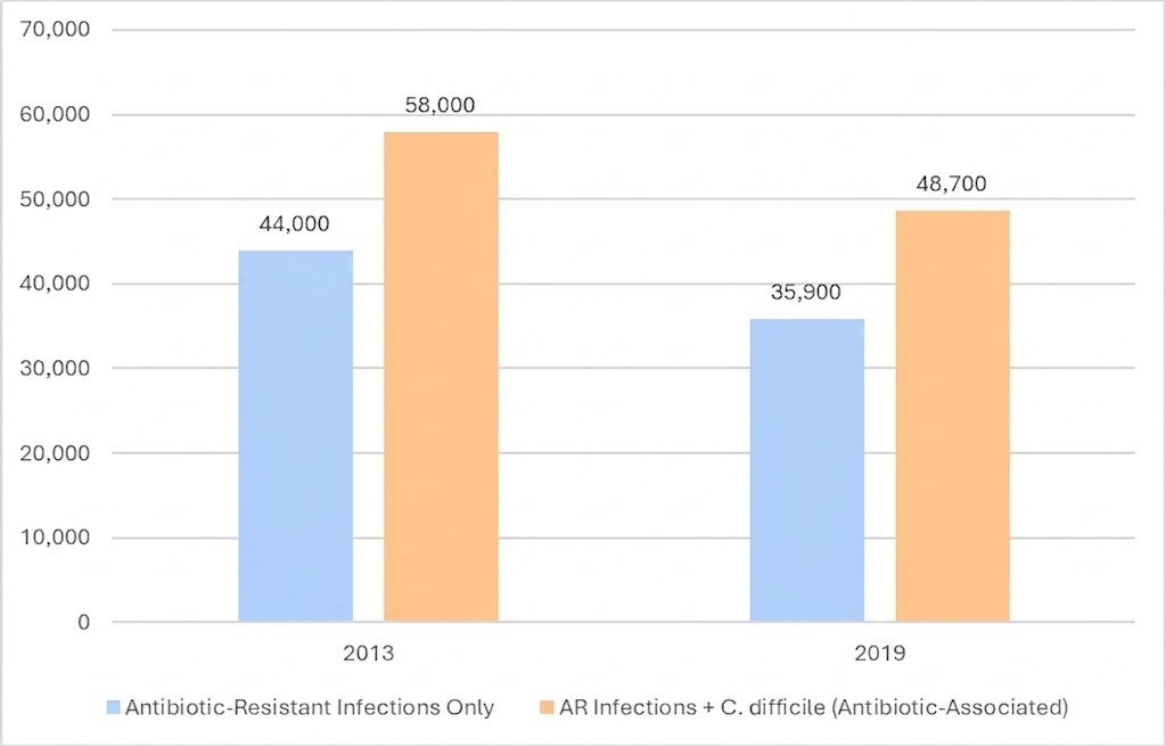
a. The Extensive Use of Antibiotics in Animal Agriculture Has Led to A Public Health Crisis

Effective antibiotics are precious medicines. They are critical for treating the myriad bacterial diseases that virtually everyone gets at some point (e.g. Strep Throat). Effective antibiotics are also essential for surgery, chemotherapy, organ transplantation, and the care of premature infants.[34] In the past, before resistance was commonplace the contraction of a bacterial infection was solvable. Now the contraction of many, once routine bacterial infections, can turn into life-threatening problems as the result of antibiotic overuse and misuse and the resultant increase in antibiotic resistance.

When bacteria develop resistance, antibiotics lose their effectiveness—resulting in more frequent, more severe infections, as well as higher rates of hospitalization and death. The CDC recognizes antibiotic resistance as "an urgent global public health threat."[35] Already, at least 2.8 million drug-resistant infections occur in the United States each year.[36] A recent Lancet study estimated that in 2021, antibiotic-resistant bacteria caused about 1 million deaths worldwide and contributed to more than 4.5 million deaths overall.[37]

[34] Ramanan Laxminarayan et al., *Antibiotic Resistance–The Need for Global Solutions*, 13 Lancet Infectious Diseases 1057 (2013).
[35] *About Antimicrobial Resistance*, CDC (Jan. 31, 2025), https://www.cdc.gov/antimicrobial-resistance/about/index.html.
[36] CDC, *Antibiotic Resistance Threats in the United States, 2019*, at vii (2019), https://www.cdc.gov/antimicrobial-resistance/media/pdfs/2019-ar-threats-report-508.pdf.
[37] GBD 2021 Antimicrobial Resistance Collaborators, *Global Burden of Bacterial Antimicrobial Resistance in 1990-2021: A Systemic Analysis with Forecasts to 2050*, 404 The Lancet 1199 (2024).

Figure 6. U.S. Deaths from Antibiotic-Related Infections per CDC Formal Threat Assessments[38]

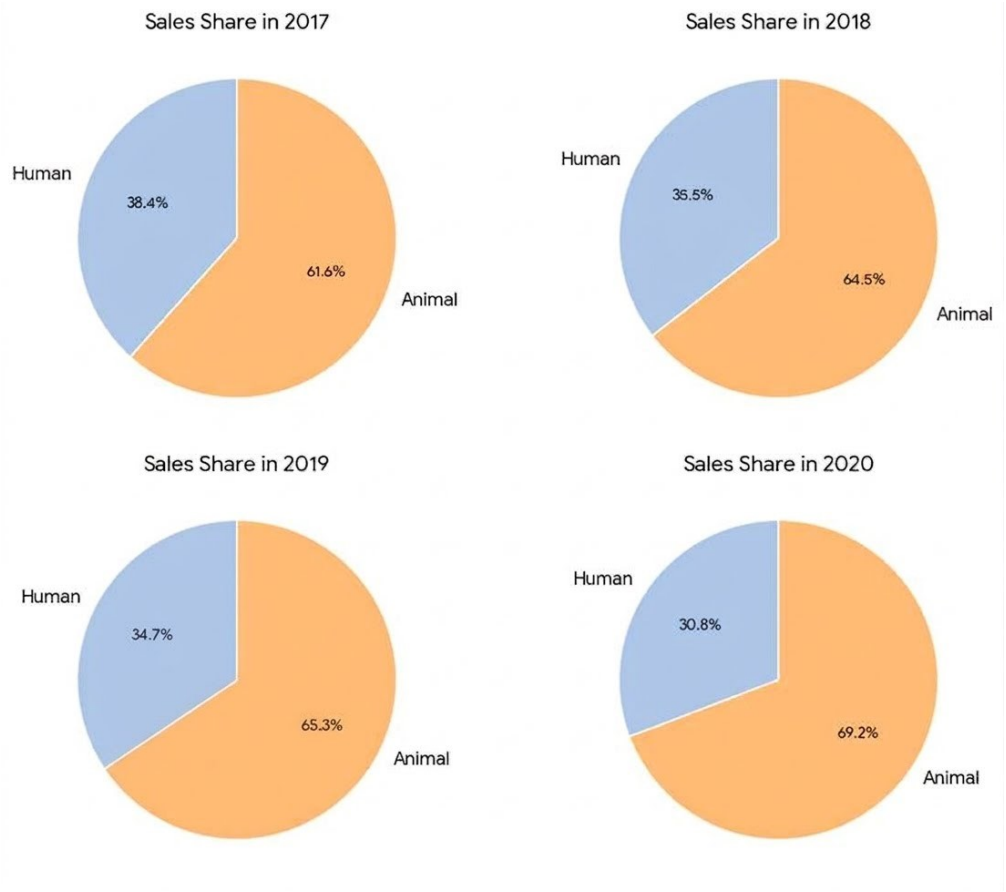


Ongoing overuse and misuse are making our limited supply of antibiotics less and less effective when they are most needed, including in the U.S. An estimated two-thirds of all MIAs in the U.S. are sold for use in food-producing animals, as opposed to those used for treating sick people.[39]

[38] CDC, *Antibiotic Resistance Threats in the United States 2019*, at 3, 6, 17 (2019), https://www.cdc.gov/antimicrobial-resistance/data-research/threats/index.html. The blue bars reflect deaths from antibiotic-resistant infections only. The orange bars add *Clostridioides difficile* (*C. diff*) deaths. Although *C. diff* bacteria are not themselves typically antibiotic-resistant, *C. diff* infections are caused by antibiotic use: broad-spectrum antibiotics disrupt the normal gut microbiome, allowing *C. diff* to proliferate and produce toxins that cause severe and sometimes fatal colitis. *C. diff* is therefore an independent and serious harm attributable to antibiotic overuse, and its inclusion provides a more complete picture of the total mortality burden. CDC classifies *C. diff* as an "urgent threat" in its AR Threats Reports alongside drug-resistant pathogens. *About C. diff*, CDC (May 13, 2026), https://www.cdc.gov/c-diff/about/index.html.

[39] David Wallinga, *Antibiotic Use Remains Far Too Intensive in U.S. Livestock: By Contrast, Falling Rates of Medical Use Suggest More Effective Stewardship*, NRDC (Sep. 11, 2023), https://www.nrdc.org/bio/david-wallinga-md/antibiotic-use-remains-far-too-intensive-us-livestock.

Figure 7. U.S. Antibiotic Sales for Use in Food-Producing Animals vs. Human Medicine (2017-2020).[40]



Yet, public health authorities, including FDA, have known for decades that the use of antibiotics in livestock and poultry production contributes to the development and spread of antibiotic-resistant bacteria transmissible to people. Over the last two decades an ever-growing body of scientific research has confirmed that the omnipresent bacteria living within animal agriculture operations are routinely exposed to antibiotics, which select for genes conferring resistance – present due to mutation, gene transfer, or through clonal spread. The result is a bacterial population highly enriched with antibiotic-resistant genes, making livestock raising operations antibiotic resistance hotspots comparable to other environments with high antibiotic use, such as hospitals and long-term care facilities. Through numerous routes of exposure, these resistant pathogens often transfer from animals to people presenting a grave health risk to both.

[40] *Id.* Human sales data was obtained by IQVIA and provided by One Health Trust. FDA does not track antibiotic use, so researchers use sales data as the best available indication of use.

b. FDA Must Prevent the Extensive Use of Antibiotics in Animal Agriculture

While all antibiotic use contributes to antibiotic resistance, uses other than for treatment or control of disease in food producing animals are especially problematic. These uses involve administering antibiotics to large groups of clinically healthy animals over extended periods of time. Unfortunately, most antibiotics presently sold for use in animals in the U.S. are administered to groups of animals in feed (65%) or water (28%).

FDA, which regulates the use of antibiotics in U.S. livestock, is required to withdraw its approval of animal drug uses that are "not shown to be safe" for human or animal health. A robust body of scientific evidence demonstrates that the extensive use of MIAs in food-producing animals without diagnosed disease or for long durations is not shown to be safe for human health. Yet, FDA continues to permit these uses of antibiotics in food animals in contravention of its legal requirements. FDA must limit the extent of use of MIAs both by withdrawing approval for certain particularly dangerous uses and by limiting the durations of remaining uses.

In 2017, FDA completed implementation of a plan to prohibit the use of MIAs in food producing animals for growth promotion, but allowed their continued use for disease prevention and for other uses beyond the treatment and control of diagnosed illness.[41] As a result, antibiotics continue to be used under conditions that are particularly conducive to the development and spread of antibiotic resistance—posing greater public health risks than limiting the use of MIAs to targeted treatment of individual sick animals with higher treatment doses for much shorter durations of time.

While antibiotic sales for use in food animals dropped after 2017, sales for use in cattle and swine have increased significantly since then and remain high. Moreover, data on indicator bacteria collected from retail meat reported by FDA do not show that overall levels of antibiotic use since 2017 have dropped sufficiently to lead to reductions in antibiotic resistance. Because a significant public health risk remains more significant FDA action is necessary.
Given the clear scientific evidence demonstrating the public health need for the Action Requested—including dozens of new expert studies cited in this Petition that were published from the year 2021 or later—and the significant human health risks posed by the overuse of medically important antibiotics in animal agriculture FDA must initiate the process to withdraw the challenged approvals.

[41] *FDA Announces Implementation of GFI #213, Outlines Continuing Efforts to Address Antimicrobial Resistance*, FDA (Jan. 3, 2017), https://wayback.archive-it.org/7993/20190423131636/https://www.fda.gov/AnimalVeterinary/NewsEvents/CVMUpdates/ucm535154.htm.

IV. LEGAL STANDARD FOR APPROVAL OF ANIMAL ANTIBIOTICS AND FDA ACTION

a. FDA Has a Mandatory Duty to Withdraw Approval of Current Unsafe Uses of MIAs in Animals

1. *FDA Has a Mandatory Duty to Withdraw Approval of Animal Drugs Not Shown to Be Safe for Human Health*

The FFDCA imposes an obligation on FDA to ensure that animal drugs are not sold for use in livestock unless they are safe for human health.[42] To this end, FDA's regulations require its Commissioner to initiate proceedings to withdraw approval for uses of an approved animal drug when new evidence shows that said uses are not shown to be safe. Specifically, 21 C.F.R. § 514.115(b) states that:

> "Commissioner shall notify in writing the person holding an application approved pursuant to section 512(c) of the act and afford an opportunity for a hearing on a proposal to withdraw approval of such application if he finds . . . New evidence . . . shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved . . . "[43]

2. *The FFDCA Sets Forth a Clear Legal Standard for Determining Whether an Animal Drug is Safe*

The FFDCA directs FDA to consider four factors to make a finding regarding the safety of an animal drug:

> (A) the probable consumption of such drug and of any substance formed in or on food because of the use of such drug,
>
> (B) the cumulative effect on man or animal of such drug, taking into account any chemically or pharmacologically related substance,
>
> (C) safety factors which in the opinion of experts, qualified by scientific training and experience to evaluate the safety of such drugs, are appropriate for the use of animal

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[42] *See generally* 21 U.S.C. § 331(a) (prohibiting "[t]he introduction or delivery for introduction into interstate commerce of any food [or] drug . . . that is adulterated"); *id.* § 360b(a)(1) (providing that "[a] new animal drug shall . . . be deemed unsafe . . . unless" FDA has approved the drug); *id.* § 351(a) (providing that a drug "shall be deemed to be adulterated . . . (5) if it is a new animal drug which is unsafe within the meaning of section 360b of this title"); *id.* § 360b(d)(1), (e)(1)(B).

[43] *See* 21 C.F.R. § 514.115(b). In *NRDC v. FDA*, a divided panel found that 21 U.S.C. § 360b(e)(1) did not require FDA to initiate withdrawal proceedings upon a preliminary finding by its Secretary that a use of an animal drug is unsafe. 760 F.3d at 172. However, the "principal question presented by this appeal" was the proper interpretation of 21 U.S.C. § 360b(e)(1). *See NRDC*, 760 F.3d at 157–58. The majority briefly discussed 21 C.F.R. § 514.115, but only answered a narrow question: whether the regulation was intended to "interpret the mandate set forth by Congress in § 360b(e)(1)." *See NRDC*, 760 F.3d at 166. The majority did not address the extent to which 21 C.F.R. § 514.115(b) itself imposes obligations on FDA to initiate withdrawal procedures when new evidence that an animal drug is unsafe comes to light. The language of the regulation plainly requires withdrawal proceedings to move forward once the Commissioner makes a preliminary finding that a new animal drug is unsafe.

experimentation data, and

(D) whether the conditions of use prescribed, recommended, or suggested in the proposed labeling are reasonably certain to be followed in practice.[44]

In accordance with this statutory mandate, FDA's longstanding policy and administrative precedent require it to make a finding that an animal drug is unsafe unless "there is a 'reasonable certainty of no harm to human health' from a proposed use of the drug in food-producing animals."[45] The "standard involves a straightforward evaluation of the human safety of an animal drug; it does not encompass any weighing of costs and benefits."[46] If certain conditions are met, the Commissioner *must* make a finding that a drug is unsafe.[47]

In the analogous context of food additive uses, FDA has recently taken the position that a petitioner seeking the repeal of a use must provide the agency with "sufficient data to establish the existence of safety questions significant enough to support a finding that there is no longer a reasonable certainty of no harm from the currently approved uses."[48]

3. Current Uses of MIAs Are Unsafe Under the FFDCA

As this Petition demonstrates, there is now clearer and more abundant scientific evidence than ever showing that the use of MIAs in the absence of diagnosed disease or for long durations in animal agriculture is unsafe. All four of the FFDCA's statutory factors support this conclusion, and thus FDA must conclude that these uses are not shown to be safe. First, studies cited and discussed in the subsequent subsections of this petition demonstrate that the current routine use of MIAs when not required to control or treat a diagnosed disease make the "consumption of [these] drug[s] and of" bacteria with antibiotic resistant genes "on food" almost certain.[49] Indeed, consumption of contaminated produce and animal-based products such as eggs, meat, and milk is a key pathway through which human beings are exposed to antibiotic-resistant bacteria.[50]

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[44] 21 U.S.C. § 360b(d)(2).
[45] *See* GFI #209, at 18 (noting that the standard applies even "after approval" of a drug); FDA, *Final Decision of the Commissioner: Withdrawal of Approval of the New Animal Drug Application for Enrofloxacin in Poultry* 93–94 (July 27, 2005), https://www.regulations.gov/document/FDA-2000-N-0109-0137.
[46] *See* FDA, *Final Decision of the Commissioner: Withdrawal of Approval of the New Animal Drug Application for Enrofloxacin in Poultry* 93–94 (July 27, 2005), https://www.regulations.gov/document/FDA-2000-N-0109-0137.
[47] Indeed, recent case law confirms that an administrator's discretion is limited even where the "sole standard [in a statute] for judging [an] agency's discretion" is language directing said administrator to take action "if he finds that such action would be in the public interest." *See Jajati v. U.S. Customs & Border Prot.,* 102 F.4th 1011, 1018–19 (9th Cir. 2024) (describing holding in *Keating v. FAA*, 610 F.2d 611, 612 (9th Cir. 1979), that under such a statute, "the 'public interest' standard provides law to be applied by the administrator sufficient to permit judicial review"). Moreover, 21 C.F.R. § 514.115(b)'s inclusion of the phrase "new evidence . . . shows" would be entirely superfluous if FDA could simply ignore new evidence emerging on a drug after it is approved. *United States v. Nature*, 898 F.3d 1022, 1024 (9th Cir. 2018) (noting that courts "construe regulations, like statutes, to give effect to every word when possible").
[48] Final Brief for Respondents at 5, *Alaska Cmty. Action on Toxics v. FDA*, No. 24-1382 (D.C. Cir. filed Nov. 20, 2025).
[49] *See* 21 U.S.C. § 360b(d)(2); *see also infra* Section B.VI.b.
[50] *See* Adrian Cazeras et al., *Pre- and Postantibiotic Epoch: The Historical Spread of Antimicrobial Resistance*, 390 Sci. (2025); *infra* Section B.VI.b.1.

Second, studies cited within this petition also demonstrate that MIAs as used in animal agriculture today have a harmful "cumulative effect on man [and] animal."[51] Indeed, there are multiple additional routes of potential exposure to MIAs and antibiotic- resistant bacteria beyond that which occurs in the context of food production, preparation and handling, including, for example, exposure to antibiotics and resistant bacteria encountered in the air, soils, rivers, and streams near and downstream from animal operations.[52] Given the nature of bacteria, exposure to *any* individual MIA may select for resistance not only to that specific drug, but potentially to multiple additional MIAs, as well.[53] This is because MIAs have shared pharmacological effects across the group of drugs. Moreover, administering any MIA for long periods of time increases bacteria exposure to the MIA, cumulatively increasing the risk that a resistant strain will develop, that susceptible bacteria will die off, and that resistance genes will spread through the bacterial population, which over time shifts the population towards one where many more bacteria are resistant to many more MIAs.[54] The impact of this shift—the cumulative impact of this antibiotic use—is greater because the use of any one antibiotic may select for bacteria resistance to multiple other antibiotics.[55] Also, cumulative use of antibiotics has led to antibiotic-resistant genes increasingly being located on mobile genetic elements, e.g., plasmids, transposons, phages and integrative conjugative elements, that are more easily transferred between bacteria.[56] Thus, the likelihood that some of these bacteria infect animals at agricultural facilities or humans through one of the various routes of exposure described above grows cumulatively as more MIAs of any kind are administered. In other words, the use of MIAs in animals without diagnosed disease or for long durations in agricultural settings presents cumulative risks to man

[51] *See* 21 U.S.C. § 360b(d)(2); *see also infra* Section B.VI.b.
[52] *See infra* Section B.VI.b.1.
[53] Exposure to one MIA can create resistance to another MIA due to a mechanism of resistance that allows bacteria to pump out multiple different antibiotics or modify a shared bacterial target of multiple antibiotics or more broadly a single bacteria may have genes to multiple antibiotics so using anyone of the antibiotics will select for all of the others this often occurs on mobile genetic elements that are readily shared between bacteria and use of antibiotics increases the ability of bacteria to share. *See also infra* Sections B.VI.a, b.
[54] *See infra* Sections B.VI, VII.
[55] *See, e.g.,* Manao Ozawa et al., *Role of Plasmids in Co-Selection of Antimicrobial Resistances Among Escherichia Coli Isolated from Pigs*, 20 Foodborne Pathogens & Disease 435 (2023); E.A. Taylor et al., *Use of Critically Important Antimicrobial Classes Early in Life May Adversely Impact Bacterial Resistance Profiles During Adult Years: Potential Co-Selection for Plasmid-Borne Fluoroquinolone and Macrolide Resistance via Extended-Spectrum Beta-Lactam Use in Dairy Cattle*, 72 Letters Applied Microbiology 220 (2021); Andrea Laconi et al., *Amoxicillin and Thiamphenicol Treatments May Influence the Co-Selection of Resistance Genes in the Chicken Gut Microbiota*, 12 Sci. Reps. (2022); Kazuki Harada et al., *Role of Coresistance in the Development of Resistance to Chloramphenicol in Escherichia Coli Isolated from Sick Cattle and Pigs*, 67 Am. J. Veterinary Rsch. 230 (2006); Rikki Franklin Frederiksen et al., *Genomic Characterization of Vancomycin-Resistant Enterococci in Norwegian Poultry*, 20 PLoS One (2025); Sarah Wendlandt et al., *Multidrug Resistance Genes in Staphylococci from Animals That Confer Resistance to Critically and Highly Important Antimicrobial Agents in Human Medicine*, 23 Trends Microbiology 44 (2015); Neena Kanwar et al., *Impact of Treatment Strategies on Cephalosporin and Tetracycline Resistance Gene Quantities in the Bovine Fecal Metagenome*, 4 Sci. Reps. (2014); Nicole Ricker et al., *Toward Antibiotic Stewardship: Route of Antibiotic Administration Impacts the Microbiota and Resistance Gene Diversity in Swine Feces*, 7 Frontiers Veterinary Sci. (2020); *infra* Sections B.VI, VII.
[56] Bethany J. Cross, Sally R. Partridge & Anna E. Sheppard, *Impacts of Mobile Genetic Elements on Antimicrobial Resistance Genes in Gram-Negative Pathogens: Current Insights and Genomic Approaches*, 302 Microbiological Rsch. (2026).

and animal alike.[57] Indeed, this more recent extensive use of antibiotics has even accelerated the processes that bacteria use to acquire and share resistance.[58]

Third, "safety factors which in the opinion of experts, qualified by scientific training and experience to evaluate the safety of such drugs, are appropriate for the use of animal experimentation data" do not militate in favor of a finding that the challenged uses of MIAs are safe. A "safety factor" is a margin of safety on top of a no effect level for a drug. For example, with respect to the toxicity of chemicals FDA determines a no effect level based on available data, and then adds one or more safety factors (usually ten-times safety factors) on top of the no effect level. Safety factors recognize that the data are often incomplete. For example, there may be limited human data, or no data specifically to the most vulnerable populations. These safety factors are therefore intended to ensure that lack of data does not lead to safety gaps and that all people are protected.[59] Here, while FDA employed safety factors when assessing the acute toxicity of antibiotics, it applied no safety factors when assessing the long-term development of antibiotic resistance. FDA ignored the profound precautionary approach of the FFDCA as embodied in these safety factors with respect to a widely harmful impact. This failure, especially given the overwhelming evidence (discussed below) that the routine preventive use of antibiotics significantly contributes to antimicrobial resistance in humans,[60] further confirms that the use of MIAs in the absence of diagnosed disease or for long durations cannot be found to be safe. Rather than ensuring safety as the law requires, the challenged approvals allow high degrees of risk by permitting the overuse of MIAs in animal agriculture under circumstances where the drugs are not needed and particularly likely to cause harm.

Finally, studies show that "the conditions of use prescribed, recommended, or suggested in the proposed labeling [for MIAs used in animal agriculture] are [far from] certain to be followed in practice."[61] Research demonstrates that "[w]hile most antibiotic use in livestock requires a prescription or a veterinary feed directive from a veterinarian, individual decisions on administration are often made by farmers."[62] As documented in a 2021 paper on perceptions and attitudes of an international group of veterinarians regarding the use of antibiotics on dairy farms, farmers, rather than following veterinary directions, in practice "appear to be an

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[57] *See infra* Sections B.VI, VII.

[58] Recent research has shown that the extensive use of antibiotics in humans and animals over the last 70 years has modified how bacteria share genes leading them to be able to efficiently spread genes conferring resistance to large numbers of antibiotics at a same. The use of antibiotics stimulated the evolution of plasmids, causing antibiotic resistance genes to increasingly appear on them. Consequently, plasmids have started recombining with other plasmids, increasing their size and incorporating other mobile genetic elements like transposons and ICEs which allow them to more easily spread resistance genes. These plasmids differ in both size and in the number of resistance genes carried from plasmids than occurred before antibiotic use became widespread. Adrian Cazares et al., *Pre- and Postantibiotic Epoch: The Historical Spread of Antimicrobial Resistance*, 390 Sci. (2025).

[59] FDA, *Guidance for Industry #3: General Principles for Evaluating the Human Food Safety of New Animal Drugs Used in Food-Producing Animals* 12 (2022), https://www.fda.gov/media/70028/download.

[60] This petition uses the terms "antibiotic" and "antimicrobial" interchangeably to refer to any man-made or naturally occurring molecule of low molecular weight that kills bacteria or inhibits their growth. *See* Michael R. Gillings, *Evolutionary Consequences of Antibiotic Use for the Resistome, Mobilome, and Microbial Pangenome*, 4 Frontiers in Microbiology 1, 1 (2013).

[61] 21 U.S.C. § 360b(d)(2).

[62] Sameer J. Patel et al., *Antibiotic Stewardship in Food-Producing Animals: Challenges, Progress, and Opportunities*, 42 Clinical Therapeutics 1649 (2020).

important source of pressure for veterinarians, driving them to prescribe antibiotics when deemed unnecessary."[63] Indeed, for feed antibiotics, FDA rules allow a veterinarian to write a single veterinary order that does not expire for six months[64] and that can be used for multiple groups of animals in multiple facilities,[65] and at different drug dosage levels and durations;[66] all of which greatly limits the extent of veterinary oversight, and gives, the farmer, not the veterinarian control over the dosage level, duration, and timing of when animals are to be given the drug. Withdrawing approval for these long-duration, relatively open-ended uses and allowing use only for treatment or control of a diagnosed illness will greatly limit the potential for abuse or not following the prescription. Furthermore, experience with human antibiotic use—where it is well documented that a substantial number of people prescribed antibiotics fail to adhere to prescribed antibiotic treatment[67]—also indicates that noncompliance with veterinary instructions for antibiotic use is highly likely.[68]

Thus, the factors taken together necessitate a conclusion that the uses of MIAs challenged in this petition are not shown to be safe.

4. FDA Has Refused to Withdraw Unsafe Uses of MIAs, Opting Instead for a Program of Voluntary Compliance

In light of the evidence, FDA cannot plausibly conclude that it is reasonably certain that current uses of MIAs causes no harm. Yet, rather than withdraw its approval of unsafe uses of MIAs, FDA on numerous occasions has asserted that urging voluntary action and half-steps, such as requiring veterinary oversight, are adequate to ensure safety. As explained further below, FDA is incorrect. These wholly voluntary measures have been ineffective and legally insufficient. A brief description of the measures is warranted, as is a summary of FDA's justifications for them.

Rather than using its full regulatory authority to restrict unsafe uses of MIAs—as required by the FFDCA—FDA has instead relied primarily on voluntary industry guidance to address the challenges of antibiotic resistance. For example:

- In 2003, FDA published GFI #152 "Evaluating the Safety of Antimicrobial New

[63] Sebastian G. Llanos-Soto et al., *Survey of Perceptions and Attitudes of an International Group of Veterinarians Regarding Antibiotic Use and Resistance on Dairy Cattle Farms*, 188 Preventive Veterinary Med. 1, 12 (2021).
[64] FDA, *Guidance for Industry #120: Veterinary Feed Directive Regulation Questions and Answers: Small Entity Compliance Guide* 7 (2024), https://www.fda.gov/media/70028/download.
[65] *Id.* at 6, 21.
[66] *Id.* at 9, 19.
[67] José María Zarauz et al., *Study of the Drivers of Inappropriate Use of Antibiotics in Community Pharmacy: Request for Antibiotics Without a Prescription, Degree of Adherence to Treatment and Correct Recycling of Leftover Treatment*, 15 Infection & Drug Resistance 6773 (2022).
[68] Aggregate statistics on adherence to veterinary prescriptions are difficult to ascertain as data reporting and analysis by federal and state government is highly limited. *See* David C. Love et al., *Dose Imprecision and Resistance: Free-Choice Medicated Feeds in Industrial Food Animal Production in the United States*, 119 Env't Health Persps. 279 (2011). One example of suggestive abuse is a USDA reported survey of pig farmers report using medically important antibiotics for growth promotion in 2021. *See* USDA, *Swine Part II: NAHMS 2021 – Reference of Management Practices on Large-Enterprise Swine Operations in the United States* tbl. C.5.g. (2021), https://www.aphis.usda.gov/livestock-poultry-disease/nahms/swine/swine-2021-part-ii-reference-management-practices-large. These farmers would have needed a prescription to use these antibiotics.

Animal Drugs with Regard to their Microbiological Effects on Bacteria of Human Health Concern," describing actions drug sponsors could take to address the safety of new antimicrobial drugs in food producing animals.[69]

- In 2009, FDA set out its thinking on what it considered appropriate use of medically important antibiotics in GFI #209.
- In 2013, FDA issued GFI #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," which outlined a voluntary approach for drug sponsors to limit certain uses of medically important antibiotics in food-producing animals—sidestepping FDA's regulatory authority to withdraw animal drugs proven unsafe.[70]
- In 2021, FDA issued GFI #263 "Recommendations for Sponsors of Medically Important Antimicrobial Drugs Approved for Use in Animals to Voluntarily Bring Under Veterinary Oversight All Products That Continue to be Available Over-the-Counter," which creates a voluntary pathway for drug makers to make label changes requiring a veterinary prescription for medically important antibiotics that do not require one.[71]
- In 2026, FDA finalized GFI #273 "Defining Durations of Use for Approved Medically Important Antimicrobial Drugs Fed to Food-Producing Animals," which likewise provides nonbinding recommendations to drug sponsors to establish appropriate durations of use for MIAs with undefined durations of use on approved labeling.[72]

Although FDA maintains that these guidance documents are sufficient to reduce the use of MIA in food producing animals, they have no binding legal effect. Rather, they do not "create or confer any rights for or on any person and does not operate to bind FDA or the public"[73] and drug makers "can use an alternative approach" because guidance is not required by regulation or statute.[74] (Indeed, evidence of continued harm-causing use makes clear these guidance documents are insufficient.)

In addition to promulgating these guidance documents, FDA has also created two five-year plans for the promotion of antibiotic stewardship in veterinary settings. These plans outline non-mandated actions to meet Agency goals, including data collection efforts for both antibiotic use and resistance and educational efforts targeted at antibiotic users.[75] While perhaps laudable, these plans, still not fully implemented, are a far cry from adequate to ensure

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[69] Original GFI #152.
[70] GFI #213.
[71] FDA, *Guidance for Industry #263: Recommendations for Sponsors of Medically Important Antimicrobial Drugs Approved for Use in Animals to Voluntarily Bring Under Veterinary Oversight All Products that Continue to Be Available Over-the-Counter* (2021) (GFI #263), https://www.fda.gov/media/130610/download.
[72] FDA, *Guidance for Industry #273: Defining Durations of Use for Approved Medically Important Antimicrobial Drugs Fed to Food-Producing Animals* (Feb. 2026) (GFI #273), https://www.fda.gov/media/191092/download.
[73] GFI #209 at 3.
[74] *See*, *e.g.*, GFI #263 at 3; GFI #209 at 3.
[75] FDA, *Supporting Antimicrobial Stewardship in Veterinary Settings: Goals for Fiscal Years 2019–2023* (2018), https://www.fda.gov/media/115776/download; FDA, *Supporting Antimicrobial Stewardship in Veterinary Settings: Goals for Fiscal Years 2024–2028* (2023), https://www.fda.gov/media/172347/download?attachment.

a reasonable certainty of no harm.

5. FDA's Program of Voluntary Compliance Is Not a Lawful Substitute for Proceedings to Withdraw Approvals for Unsafe Uses of MIAs

In May 2011, the Natural Resources Defense Council, Center for Science in the Public Interest, Food Animal Concerns Trust, Public Citizen, and the Union of Concerned Scientists sued FDA. The citizen groups argued that FDA was statutorily required to begin proceedings to withdraw approval of certain uses of penicillin and tetracyclines in livestock based on FDA's 1977 findings that those drug uses were not shown to be safe for human health. Later, the groups also challenged FDA's denial of two citizen petitions seeking the withdrawal of approval of several additional uses of antibiotics in livestock production, arguing that the petition denial was unlawful because it depended on a rationale—FDA's preference for a voluntary approach—that was divorced from the relevant statutory inquiry: whether the challenged drug uses were "shown to be safe."[76]

The District Court ruled for the citizen groups, but in 2014 a divided panel of the Second Circuit Court of Appeals reversed, declining to set aside as arbitrary and capricious "FDA's determination that its preferred program of voluntary compliance offers greater prospect for immediate and significant reductions in animal antibiotic use than" withdrawal proceedings.[77]

More than a decade later, and based on a mountain of new evidence, the Second Circuit holding is no longer tenable. As the Second Circuit itself has recognized, "decisions which are not arbitrary and capricious in the light of existing knowledge may become so by the dint of scientific advances."[78] Indeed, this Petition cites to 167 new studies published since the Second Circuit issued its decision in 2014.

Despite the partial, lackluster actions by FDA, humans are still exposed at alarming rates to antibiotic-resistant bacteria generated by the misuse of antibiotics in animal agriculture. FDA is required to consider the studies and the new evidence presented in this Petition, as it must

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[76] *See* 21 C.F.R. § 514.115(b).

[77] *See NRDC*, 760 F.3d at 175. Approximately two years later, the Natural Resources Defense Council, Center for Science in the Public Interest, Earthjustice, Food Animal Concerns Trust, Public Citizen, U.S. Public Interest Research Group, and California Public Interest Research Group submitted a petition under section 512(e) of the FFDCA to request that FDA withdraw approval of the use of medically important antibiotics in livestock and poultry for disease-prevention or growth-promotion purposes. NRDC et al., Citizen Petition to Request Withdrawal of Approval of the Use of Medically Important Antibiotics in Livestock and Poultry for Disease-Prevention or Growth-Promotion Purposes (Sep. 13, 2016), https://www.regulations.gov/document/FDA-2016-P-2737-0001. In February 2021, FDA denied the petition but acknowledged the "risk that antimicrobial resistance poses to public health." Letter from Steven Solomon, Dir. Ctr. for Veterinary Med., FDA, to Allison Johnson & Avinash Kar, NRDC, at 2 (Feb. 25, 2021), https://www.regulations.gov/document/FDA-2016-P-2737-0144. In January 2023, the Alliance of Nurses for Healthy Environments, Food Animal Concerns Trust, Natural Resources Defense Council, and Public Citizen sued FDA over the denial of the petition arguing the denial violates the APA. *See All. of Nurses for Healthy Env'ts v. FDA*, No. 8:23-cv-176 (D. Md. dismissed July 15, 2024). In July 2024, the case was dismissed due to lack of standing of the plaintiffs and without reaching the merits of the petitioners' claims under section 512(e) of the FFDCA. *See id.*

[78] *See Ala. Power Co.*, 636 F.2d at 388 n.116 (quoting *Texas v. EPA*, 499 F.2d 289, 301 n.16 (5th Cir. 1974)).

"base its decisions on the entire record."[79] When, as now, "an agency . . . is confronted with evidence that . . . the factual premises underlying its prior judgment have eroded, it must offer more to justify its decision . . . than mere conclusory statements. . . . [FDA] must provide 'assurance that [it] considered the relevant factors.'"[80]

In summary, this Petition demonstrates that FDA's decision to promulgate voluntary guidance rather than take firm regulatory action simply has not adequately reduced exposure of humans to antibiotic-resistant bacteria resulting from the approved uses of antibiotics in food-producing animals. Accordingly, the FDA commissioner must make a finding pursuant to 21 C.F.R. § 514.115(b) that the current non-therapeutic and long duration use of MIAs in food producing animals is unsafe, and thereafter initiate withdrawal proceedings.

b. FDA Has Multiple Means at Its Disposal to Reduce the Administrative Burdens Associated with Withdrawal Proceedings

In the past, FDA has concluded that formal evidentiary hearings to withdraw animal antibiotic use approvals "would take many years and would impose significant resource demands on FDA."[81] Even if this were a sufficient reason to allow a significant public health threat to continue unabated—which it is not—FDA has many tools at its disposal to comply with its obligations to end unsafe uses of MIAs. FDA must find a way to initiate withdrawal proceedings, as the agency cannot continue to fail to comply with its legal duty to ensure safety.

FDA has withdrawn approval of certain antibiotic uses several times before, and it can do so again. FDA can withdraw approval for certain animal drugs after a formal evidentiary hearing,[82] or by regulation.[83] This past practice suggests that the administrative burdens of such formal proceedings are hardly insurmountable. FDA could avail itself of various tools to reduce the administrative burdens of formal proceedings, including, for example, summary adjudication,[84] or combining similar drug products and approvals in a single hearing. Moreover, to establish facts that could be applied in multiple hearings FDA could conduct a generic rulemaking,[85] or issue an advisory opinion pursuant to 21 C.F.R. § 10.85 stating that

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[79] *Purepac Pharm. Co. v. Thompson,* 354 F.3d 877, 885 (D.C. Cir. 2004); *c.f. WWHT, Inc. v. FCC*, 656 F.2d 807, 817–18 (D.C. Cir. 1981) (noting that "the 'record' for purposes of review" of a rulemaking petition includes the petition).

[80] *C.f. Env't Health Tr. v. FCC*, 9 F.4th 893, 903 (D.C. Cir. 2021) (citations omitted) (finding denial of rulemaking petition arbitrary and capricious).

[81] Letter from Lesley Kux, Acting Assistant Comm'r for Pol'y, FDA, to Andrew Maguire, Env't Def. Fund, at 3 (Nov. 7, 2011), https://www.regulations.gov/document/FDA-2005-P-0007-0007; Letter from Lesley Kux, Acting Assistant Comm'r for Pol'y, FDA, to Sarah Klein, Ctr. for Sci. in the Pub. Interest, at 3 (Nov. 7, 2011), https://www.regulations.gov/document/FDA-1999-P-1286-0014.

[82] *See, e.g.*, FDA, *Final Decision of the Commissioner: Withdrawal of Approval of the New Animal Drug Application for Enrofloxacin in Poultry* (July 27, 2005), https://www.regulations.gov/document/FDA-2000-N-0109-0137.

[83] *See, e.g.*, Antibiotic and Sulfonamide Drugs in Animal Feeds, 37 Fed. Reg. 2444, 2444–45 (Jan. 25, 1972); Penicillin-Containing Premixes, 42 Fed. Reg. 43772, 43772 (Aug. 30, 1977); Tetracycline (Chlortetracycline and Oxytetracycline)-Containing Premixes, 42 Fed. Reg. 56264, 56288 (Oct. 21, 1977).

[84] *See* 21 C.F.R. § 514.200(c)(2) (2025).

[85] *See Heckler v. Campbell*, 461 U.S. 458, 467 (1983) ("The Court has recognized that even where an agency's enabling statute expressly requires it to hold a hearing, the agency may rely on its rulemaking authority to determine

the non-therapeutic uses of MIAs identified in this Petition are unsafe. While an advisory opinion pursuant to 21 C.F.R. § 10.85 "represents the formal position of FDA" and "may be used in administrative . . . proceedings to illustrate acceptable and unacceptable . . . standards,"[86] a generic rulemaking would be more effective and clear.

Moreover, FDA could reduce administrative burdens by eschewing evidentiary hearings. Both the FFDCA and FDA's own implementing regulations allow it to withdraw approval of an animal drug without holding a formal evidentiary hearing.[87] The statute provides that FDA "shall, after due notice and opportunity for hearing to the applicant, issue an order withdrawing approval" of an animal drug if it finds that new evidence shows that use of the drug is not shown to be safe.[88] Because the statute does not specify that the hearing must be formal, "on the record," or in accordance with section 554 of the Administrative Procedure Act (APA), a formal evidentiary hearing is not required.[89] Courts have deferred to agencies' decisions to use informal hearing procedures where a statute requires only an opportunity for a "hearing."[90]

FDA's implementing regulations likewise allow it to use informal hearings to withdraw approval of animal drugs. The regulations state that a formal evidentiary hearing is required only where the "subject matter of the regulation or order is subject by statute to an opportunity for a formal evidentiary public hearing."[91] And, as just stated, the withdrawal of animal drug approvals is not subject to such a statutory requirement. Moreover, although FDA's regulations include the Act's animal-drug-withdrawal provision in a list of statutory provisions affording "an opportunity for a formal evidentiary public hearing," the

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issues that do not require case-by-case consideration. . . . A contrary holding would require the agency continually to relitigate issues that may be established fairly and efficiently in a single rulemaking proceeding." (citations omitted)).

[86] 21 C.F.R. § 10.85(e), (j) (2025).

[87] *See generally* Lisa Heinzerling, *Undue Process at the FDA: Antibiotics, Animal Feed, and Agency Intransigence*, 37 Vt. L. Rev. 1007, 1008 (2013) (explaining that FDA "is not required to hold formal evidentiary hearings on whether approvals for certain antibiotics should be withdrawn because the drugs are not 'safe' within the meaning of the FDCA").

[88] 21 U.S.C. § 360b(e)(1)(B).

[89] *See* 5 U.S.C. § 554(a) (providing that the APA requires a formal evidentiary hearing "in every case of adjudication required by statute to be determined on the record after opportunity for an agency hearing"); *United States v. Fla. E. Coast Ry. Co.*, 410 U.S. 224, 238 (1973) (holding that the phrase "after hearing" in the Interstate Commerce Act did not trigger the APA's formal rulemaking procedures—which apply when "rules are required by statute to be made on the record after opportunity for an agency hearing," 5 U.S.C. § 553(c)—and concluding that those formal procedures are triggered when Congress uses the words "on the record" or "other statutory language having the same meaning"); *Am. Tel. & Tel. Co. v. FCC*, 572 F.2d 17, 22 (2d Cir. 1978) (observing that, since Florida East Coast Railway, the words "on the record" are "a 'touchstone test' for the applicability of the APA's trial-type procedures" (quoting Mobil Oil Corp. v. Fed. Power Comm'n, 483 F.2d 1238, 1250 (D.C. Cir. 1973))); *City of West Chicago, Ill. v. U.S. Nuclear Regul. Comm'n*, 701 F.2d 632, 641, 644 (7th Cir. 1983) (holding that in adjudication, as in rulemaking, the APA's formal hearing requirements do not apply if Congress does not use the words "on the record," or otherwise "clearly indicate its intent" to trigger those formal requirements).

[90] *See Dominion Energy Brayton Point, LLC v. Johnson*, 443 F.3d 12, 18–19 (1st Cir. 2006), overruling *Seacoast Anti-Pollution League v. Costle*, 572 F.2d 872 (1st Cir. 1978); *Chem. Waste Mgmt. v. EPA*, 873 F.2d 1477, 1482 (D.C. Cir. 1989) ("[A]n agency that *reasonably* reads a simple requirement that it hold a 'hearing' to allow for informal hearing procedures must prevail under the second step of *Chevron*." (emphasis in original)); *Sibley v. U.S. Dep't of Educ.*, 913 F. Supp. 1181, 1186 n.3 (N.D. Ill. 1995).

[91] 21 C.F.R. § 10.50(a)(1) (2025).

regulations also state that the list "imparts no right to a hearing where the statutory section provides no opportunity for a hearing," [92] as is the case for animal drug withdrawal proceedings.

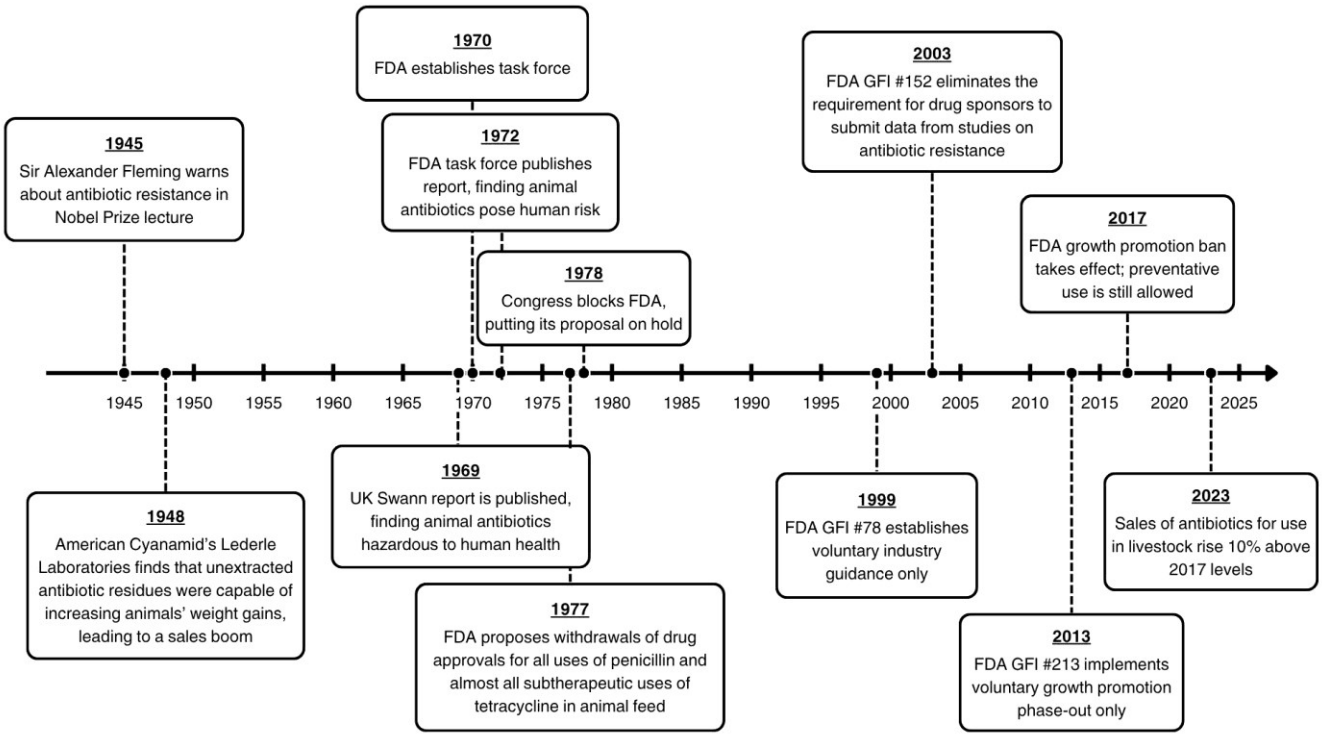
V. PAST FDA ACTIONS ARE INADEQUATE TO REDUCE THE RISK OF HARM FROM THE ROUTINE USE OF ANTIBIOTICS IN ANIMAL AGRICULTURE TO SAFE LEVELS

a. FDA Has Long Recognized the Risk of Routine Animal Use of Antibiotics on Human Health, and Yet Has Never Taken Adequate Action.

For over 50 years, FDA has had concerns or known that the use of antibiotics in animal feed for purposes other than treatment or control of disease cannot, in any normal sense of the word, be considered safe. Yet, despite that understanding and despite FDA's legal duty to ensure that animal drugs are used safely, the agency has dithered, delayed, backtracked, and taken only partial steps that—based on clear evidence—have been inadequate. This sordid history of delay has led to the deaths and sickness of millions of Americans.

[92] *Id.* § 10.50(c).

Figure 8. FDA Regulatory History on Antibiotic Use in Food-Producing Animals (1945–2023)[93]



1. *From the Beginning, the Routine Use of Antibiotics in Animal Feed and Water Was Not for Animal Health and Was Recognized as Dangerous to Human Health*

The routine use of antibiotics in animal feed and water did not arise from agricultural necessity. It was developed and commercially promoted by the pharmaceutical industry beginning in the late 1940s after a scientists at American Cyanamid discovered that adding subtherapeutic doses

[93] *Sir Alexander Fleming – Nobel Prize Lecture*, The Nobel Prize, https://www.nobelprize.org/prizes/medicine/1945/fleming/lecture/ (last visited Mar. 31, 2026); Claas Kirchhelle, *Pharming Animals: A Global History of Antibiotics in Food Production (1935-2017)*, 4 Palgrave Comm'cns (2018); Michael Swann et al., Joint Comm. on the Use of Antibiotics in Animal Husbandry & Veterinary Med., *Report Presented to Parliament by the Secretary of State for Social Services, the Secretary of State for Scotland, the Minister of Agriculture, Fisheries and Food and the Secretary of State for Wales by Commands of Her Majesty* (1969), https://iiif.wellcomecollection.org/pdf/b32170610. FDA first formally acknowledged the human health risk of agricultural antibiotic use in 1972, proposed to act in 1977, and was blocked by Congress. FDA, *Food and Drug Administration Antibiotic Task Force Report*, 51 Poultry Sci. 720 (1972) (stating that FDA established a task force to study the implications from the use of antibiotics in animal feeds to human and animal health in April 1970); Walter J. Armbruster & Tanya Roberts, *The Political Economy of US Antibiotic Use in Animal Feed*, Food Safety Econ. 293 (2018). It then spent more than three decades relying on voluntary industry compliance. The 2017 growth-promotion ban left the substantially overlapping practice of routine preventive use entirely intact. GFI #78; Original GFI #152; GFI #213; Penicillin-Containing Premixes; Opportunity for Hearing, 42 Fed. Reg. 43772 (Aug. 30, 1977); Bennett Rosenberg, *Growing Use of Antibiotics in Factory-Farmed Animals Threatens Life-Saving Medications*, Env't Working Grp. (Nov. 13, 2024), https://www.ewg.org/news-insights/news/2024/11/life-saving-antibiotics-jeopardy-growing-use-factory-farmed-animals.

of the antibiotic aureomycin (chlortetracycline) to chicken feed accelerated animal growth.[94] Drug companies, already manufacturing antibiotics at scale for human medicine, recognized a substantial new market and moved aggressively to promote agricultural use worldwide.[95] Today over 26 million pounds of antibiotics are sold for use in livestock per year.[96] The three companies that have dominated the contemporary U.S. animal antibiotic market—Zoetis[97] (spun off from Pfizer in 2013), Merck Animal Health, and Elanco (founded as a division of Eli Lilly and Company in 1954 and spun off in 2019)—are the direct corporate descendants of the pharmaceutical companies that created and profited from this market.[98]

This commercialization occurred despite explicit and early warnings. In his 1945 Nobel Prize acceptance speech, Alexander Fleming—the discoverer of penicillin—warned that sub-lethal antibiotic exposure would select for resistant bacteria, a phenomenon he had already observed in his laboratory: "There is the danger," Fleming said, "that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant."[99] By the early 1950s, scientists had documented resistance in food animals receiving antibiotic feed supplements.[100] In 1965, a roundtable of prominent infectious disease specialists warned that antibiotic resistance was rising and the pipeline of effective drugs was insufficient to keep pace.[101] In 1969, a British committee studying agricultural antibiotic use concluded that feeding antibiotics preventatively to apparently healthy farm animals posed hazards to human health and that it could find no "excuse in logic or theory" for the practice.[102] The World Health

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[94] Maryn McKenna, *Big Chicken: The Incredible Story of How Antibiotics Created Modern Agriculture and Changed the Way the World Eats* 45–51 (2017) (describing experiments at Lederle Laboratories in December 1948); *see also* J.J. Dibner & J.D. Richards, *Antibiotic Growth Promoters in Agriculture: History and Mode of Action*, 84 Poultry Sci. 634 (2005).

[95] Claas Kirchhelle, *Pharming Animals: A Global History of Antibiotics in Food Production (1935-2017)*, 4 Palgrave Comm'cns (2018); *see*, *e.g.*, Maryn McKenna, *Big Chicken*.

[96] FDA, *2024 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals* tbl. 2a (2025), https://www.fda.gov/animal-veterinary/antimicrobial-resistance/2024-summary-report-antimicrobials-sold-or-distributed-use-food-producing-animals.

[97] Phibro Animal Health acquired Zoetis's medicated feed additive portfolio and certain water soluble products and related assets in 2024, but continues to sell other veterinary antibiotic products.

[98] *Leading Animal Health Companies in 2024, Based on Revenue*, Statista, https://www.statista.com/statistics/260190/leading-animal-health-providers-based-on-revenue/?srsltid=AfmBOorqApbZPQyMbdRaNwUJ-7touvIo0j5Getniiu30QEk_7yDW-oC0 (last visited Apr. 17, 2026); *Our Story*, Zoetis, https://www.zoetis.com/our-company/our-story/history (last visited May 5, 2026); *Our Story*, Merck, https://www.merck-animal-health.com/about-us/our-story/ (last visited May 5, 2026); *Going Beyond for 70 Years*, Elanco, https://www.elanco.com/en-us/about-us/our-journey (last visited Apr. 17, 2026).

[99] *Sir Alexander Fleming – Nobel Prize Lecture*, The Nobel Prize, https://www.nobelprize.org/prizes/medicine/1945/fleming/lecture/ (last visited Mar. 31, 2026); *see also The Unseen Enemy: Navigating Antimicrobial Resistance*, The Nobel Prize, https://www.nobelprize.org/the-unseen-enemy-navigating-antimicrobial-resistance/ (last visited Apr. 17, 2026).

[100] Mortimer P. Starr & Donald M. Reynolds, *Streptomycin Resistance of Coliform Bacteria from Turkeys Fed Streptomycin*, 41 Am. J. Pub. Health & Nation's Health 1375 (1951); Scott H. Podolsky, *The Evolving Response to Antibiotic Resistance (1945–2018)*, 4 Palgrave Commc'ns (2018).

[101] Brad Spellberg & David N. Gilbert, *The Future of Antibiotics and Resistance: A Tribute to a Career of Leadership by John Bartlett*, 59 Clinical Infectious Diseases S71 (2014) (citing 1965 roundtable of prominent infectious disease experts).

[102] Michael Swann et al., Joint Comm. on the Use of Antibiotics in Animal Husbandry & Veterinary Med., *Report Presented to Parliament by the Secretary of State for Social Services, the Secretary of State for Scotland, the Minister of Agriculture, Fisheries and Food and the Secretary of State for Wales by Commands of Her Majesty*, at 34 (1969), https://iiif.wellcomecollection.org/pdf/b32170610; *see* Claas Kirchhelle, *Swann Song: Antibiotic*

Organization (WHO) made similar findings as early as 1959.[103] These science-based warnings were consistent and credible, but consistently ignored by the pharmaceutical and agricultural industries.

Pharmaceutical industry opposition to limits on the routine preventive use of antibiotics continues to the present and limits FDA's ability to act. When Congress considered new legislation in the last decade, pharmaceutical companies spent at least $135 million lobbying against limits on antibiotic use in animal feed in 2009 alone, with agribusiness companies spending an additional $70 million in the same year.[104] In 2013 and 2014, the leading veterinary pharmaceutical manufacturers—including Zoetis and Elanco—spent millions more lobbying against three separate legislative proposals to restrict agricultural antibiotic use.[105] The industry's trade association, the Animal Health Institute, meanwhile publicly testified before Congress that there is "not unequivocal evidence" of a connection between agricultural antibiotic use and human resistance—directly contradicting the findings of its own industry-funded study published in the New England Journal of Medicine.[106]

These lobbying efforts have been supplemented by marketing campaigns that aim to both encourage antibiotic overuse in animal agriculture, and also downplay concerns about public health harms resulting from this overuse. For example, a 2019 New York Times Report found that Elanco developed a brochure encouraging farmers to prophylactically give antibiotics to whole herds of pigs.[107] The company also funded a consumer-facing campaign which side-stepped the issue of antibiotic resistance altogether—suggesting that antibiotic use in animal agriculture is safe because meat and milk are "free of harmful residues from antibiotics."[108] A

Regulation in British Livestock Production (1953–2006), 92 Bull. History Med. 317 (2018); *UK Faces Weakest Antibiotics Regulations in Europe*, Compassion in World Farming (Nov. 20, 2019), https://www.ciwf.org.uk/news/2019/11/uk-faces-weakest-antibiotics-regulations-in-europe.

[103] Scott H. Podolsky, *The Evolving Response to Antibiotic Resistance (1945–2018)*, 4 Palgrave Commc'ns (2018) (documenting WHO expert meetings on antibiotic resistance beginning in 1959).

[104] Walter J. Armbruster & Tanya Robert, *The Political Economy of US Antibiotic Use in Animal Feed*, *in Food Safety Economics* (2018).

[105] Amy Nordrum & Elizabeth Whitman, *Antibiotic Resistance: How Livestock Lobbyists and Drug Companies Hinder the US Fight Against Superbugs*, Int'l Bus. Times (Apr. 29, 2015), https://www.ibtimes.com/antibiotic-resistance-how-livestock-lobbyists-drug-companies-hinder-us-fight-against-1901499 (reporting Zoetis spent $1.01 million and Elanco spent $200,000 lobbying against antibiotic restriction legislation in 2013–2014, with the Animal Health Institute spending an additional $130,000).

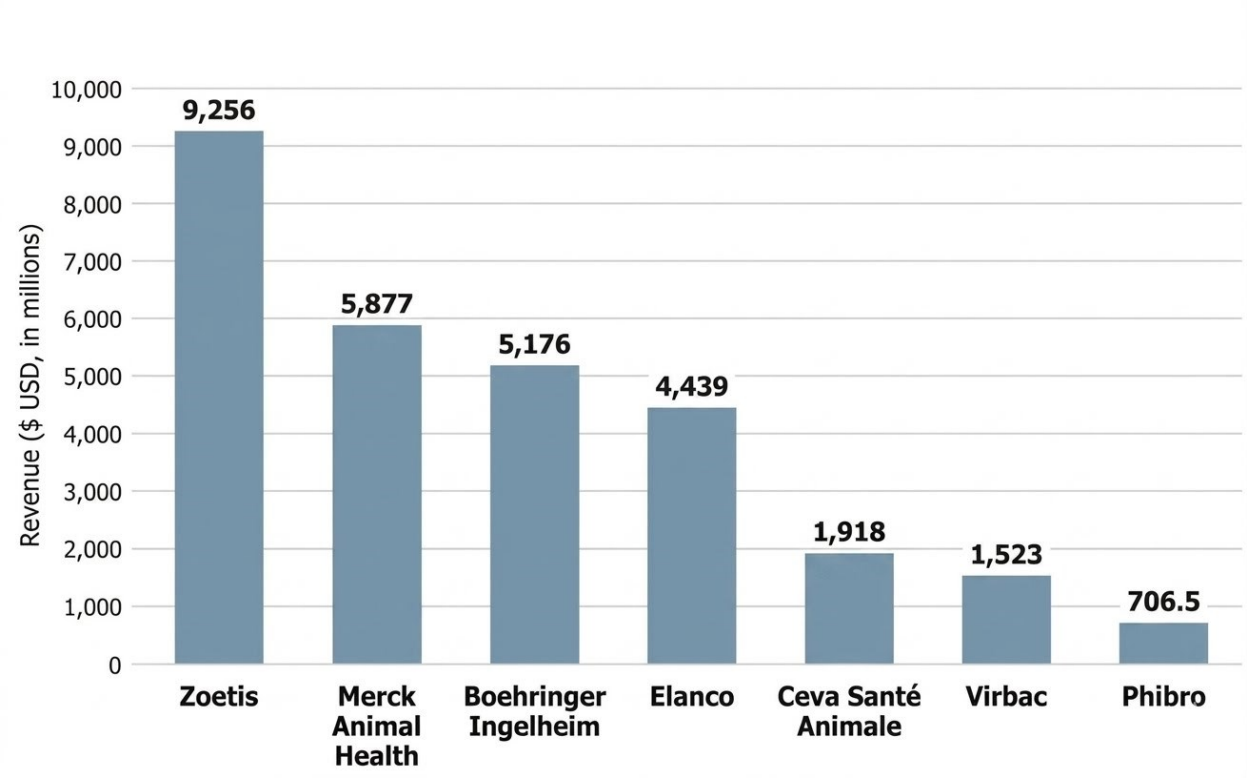
[106] *Antibiotic Resistance and the Use of Antibiotics in Animal Agriculture: Hearing Before the Subcomm. on Health of the Comm. on Energy & Com.*, 111th Cong. 226 (2010), https://www.govinfo.gov/content/pkg/CHRG-111hhrg77921/pdf/CHRG-111hhrg77921.pdf (statement of Richard Carnevale, D.V.M., Vice President, Regul., Sci. & Int'l Affs., Animal Health Inst.); *contra* S.B. Levy, G.B. FitzGerald & A.B. Macone, *Changes in Intestinal Flora of Farm Personnel After Introduction of a Tetracycline-Supplemented Feed on a Farm*, 295 New England J. Med. 583 (1976) (industry-funded study demonstrating transmission of resistant bacteria from antibiotic-fed animals to farm workers and their families).

[107] Michaela Herrmann, *'Narratives of Delay': How the Animal Pharma Industry Resists Moves to Curb the Overuse of Antibiotics on Farms*, Sentient (Jan. 15, 2024), https://sentientmedia.org/animal-pharma-industry-overuse-of-antibiotics/.

[108] Ben Stockton, Madlen Davies & Andrew Wasley, *Diversion Tactics: How Big Pharma Is Muddying the Waters on Animal Antibiotics*, The Guardian (June 19, 2018), https://www.theguardian.com/environment/2018/jun/19/animal-antibiotics-calm-down-about-your-chicken-says-big-pharma.

2021 report by the FAIRR Initiative suggests that such marketing practices are widespread.[109] The report found that none of the ten largest publicly listed animal health companies has a policy on responsibly marketing antibiotics for use in animal agriculture, and that marketing practices are driving the misuse of these drugs.[110]

Figure 4. Estimated Global Sales of Seven Major Animal Health Companies (2024, Net Manufacturer Revenue for Animal Health)[111]



2. Decades ago, FDA Acknowledged that the Use of Antibiotics in Agriculture Is Unsafe.

In 1970, recognizing that the use of antibiotics in livestock production increases the prevalence of antibiotic resistance in food-borne pathogens and other bacteria, FDA established a task force to evaluate the use of antibiotics in animal feed. The task force's 1972 report reached conclusions that remain highly relevant today: the use of antibiotics especially for growth promotion or at doses intended for prevention rather than treatment of diagnosed disease in

[109] *$47-Billion Animal Health Sector Fuelling Irresponsible Antimicrobial Use in Meat Supply Chains*, FAIRR (July 22, 2021), https://www.fairr.org/news-events/press-releases/animal-health-sector-fuelling-irresponsible-antimicrobial-use-in-meat-supply-chains.

[110] *Id*.; *see also* Lisa Held, *Ads for Livestock Antibiotics Fly in the Face of FDA Rules. Will the Agency Step In?*, Civil Eats (Jan. 25, 2022), https://civileats.com/2022/01/25/marketing-advertising-livestock-antibiotics-fda-rules-zoetis-aureomycin-resistance-public-health/ (noting that Zoetis marketed Aureomycin, which contains chlortetracycline, for preventative use in repeated five-day "pulses," ignoring FDA's five-day limit for chlortetracycline).

[111] *See supra* note 20.

animals selects for resistance in bacteria in the animals, resistant bacteria contaminate meat, and resistance originating in animals can be a source of resistant infections in humans.[112] The task force flagged as problematic many of the antibiotics still now under scrutiny.[113] The task force also found that the continuous feeding of antibiotics to animals could "compromise" the treatment of disease and identified an additional risk: such practices could increase the prevalence of the foodborne pathogen *Salmonella* in treated animals.[114]

The task force recommended that "antibiotics which select for bacteria resistant to the antibiotics most critically needed for therapy of man and animals be prohibited from use in animal feeds" and that any subtherapeutic or growth promotion uses of other antibiotics that are also used in humans be revoked, unless specific data were submitted addressing the health risks.[115] In 1973, FDA issued a regulation warning that it would propose to withdraw all approvals for subtherapeutic uses of antibiotics defined to include disease prevention and growth promotion in animal feed within two years, unless drug sponsors and other interested parties submitted data "which resolve[d] conclusively the issues concerning [the drugs'] safety to man and animals . . . under specific criteria" established by FDA.[116] The criteria required sponsors of subtherapeutic antibiotics used in feed to demonstrate that their use neither increased resistance in *Salmonella* or *E. coli* in treated animals nor resulted in greater shedding of *Salmonella* by those animals.[117] Sponsors were required to submit all information to FDA on the impact of their drug(s) on the "salmonella reservoir" in animals by specific dates depending on the class of drug.[118]

Four years later, in 1977, the Director of FDA's Bureau of Veterinary Medicine concluded that certain disease prevention and growth promotion uses of penicillin and tetracyclines in livestock were "not shown to be safe under the conditions of use prescribed," and FDA said it would propose to withdraw "subtherapeutic" uses,[119] which it defined in the regulation as "increased rate of [weight] gain, disease prevention, etc."[120] FDA then issued notices of opportunities for a

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[112] *See* Antibiotic and Sulfonamide Drugs in Animal Feeds, 37 Fed. Reg. at 2444–45.

[113] Of the New Animal Drug Applications (NADAs) listed in the 1977 Notice of Opportunity for a Hearing, Tetracycline (Chlortetracycline and Oxytetracycline)-Containing Premixes, 42 Fed. Reg. at 56265, the following NADAs are still approved for continuous use in at least one species: 008-804, 035-688, 046-699, 048-761, 049-287. *Animal Drugs*, FDA, https://animaldrugsatfda.fda.gov/adafda/views/#/search (last visited Feb. 12, 2026).

[114] Antibiotic and Sulfonamide Drugs in Animal Feeds, 37 Fed. Reg. at 2445

[115] *Id.* The separation between antibiotics used in human medicine, MIAs in this petition, and a further characterization of some as "critically needed" is included in FDA's current approach to antibiotic resistance management which restricts use of MIAs more than other antibiotics and ranks MIAs by their medical importance.

[116] Antibiotic and Sulfonamide Drugs in the Feed of Animals, 38 Fed. Reg. 9811, 9813 (Apr. 20, 1973) (codified at former 21 C.F.R. § 135.109; later renumbered as 21 C.F.R. § 558.15). FDA said it would propose to withdraw "subtherapeutic" uses, which it defined in the regulation as "increased rate of [weight] gain, disease prevention, etc." *See id.* FDA rescinded the regulation earlier this year, stating that it had "other strategies for assessing the safety of antimicrobial new animal drugs with regard to their microbiological effects on bacteria of human health concern." New Animal Drugs for Use in Animal Feeds; Removal of Obsolete and Redundant Regulations, 81 Fed. Reg. 11664, 11664 (Mar. 7, 2016).

[117] J.M. Gilbert, *A Review of Studies Submitted to CVM Assessing the Effects of Sub-Therapeutic Use of Antimicrobial Drugs on the Salmonella Reservoir in Food Producing Animals* 4–10 (2001). Attached as Appendix B.

[118] 21 C.F.R. § 558.15(b) (2025).

[119] Penicillin-Containing Premixes, 42 Fed. Reg. at 43792; Penicillin in Animal Feeds, 42 Fed. Reg 43770, 43770 (Aug. 30, 1977); Chlortetracycline and Oxytetracycline in Animal Feeds, 42 Fed. Reg. 56254, 56254 (Oct. 21, 1977).

[120] Antibiotic and Sulfonamide Drugs in the Feed of Animals, 38 Fed. Reg. at 9813.

hearing, allowing impacted companies to challenge FDA's findings related to safety and efficacy.[121] Drug sponsors carried out the required studies in chickens, swine, and cattle and across all species, which showed a consistent increase in resistant *Salmonella* in treated animals compared with unmedicated controls, indicating that use of these drugs contributed to increased antibiotic resistance.[122] FDA excluded certain approvals for the subtherapeutic use of tetracycline in feed from its withdrawal orders—not because these uses were determined to be safe, but because no alternatives were available for those uses in food-producing animals.[123] These subtherapeutic uses of tetracycline exempted from withdrawal were for "control," "maintenance of weight gains," and "reduc[tion of] incidence."[124]

In 1978, after aggressive lobbying by the pharmaceutical industry,[125] Congress intervened, directing FDA to put the withdrawals on hold and to conduct further studies.[126] This directive stymied action permanently: tetracycline antibiotics in feed and water and penicillin in water continue to be the most used and second-most used antibiotics in food-producing animals respectively, measured by volume of sales.[127] While FDA failed to move forward on withdrawals of the existing approvals for these antibiotics, the agency did require studies on antibiotic resistance development for new approvals intended to be used in the feed of animals for more than 14 days.[128] Unfortunately, most of the studies had design flaws that limited their ability to detect resistance, but even so two out of three appropriately designed studies showed increased resistance and thus their applications were not approved under the proposed conditions of use.[129]

3. In the Late 1990's FDA Began Its Unsuccessful Effort to Manage the Public Health Risks of Antibiotics in Agriculture Through Voluntary Industry Compliance.

In 1999, FDA shifted its approach from regulation to industry guidance in addressing antibiotic resistance when it issued GFI #78: "Consideration of the Human Health Impact of the Microbial

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[121] Penicillin-Containing Premixes, 42 Fed. Reg. at 43772; Tetracycline (Chlortetracycline and Oxytetracycline)-Containing Premixes, 42 Fed. Reg. at 56288.
[122] Tetracycline (Chlortetracycline and Oxytetracycline)-Containing Premixes, 42 Fed. Reg. at 56275 (chickens and swine); *id.* at 56275–76 (cattle). Tetracyclines at the same dosage as some of these studies are still approved for continuous use in cattle and swine (e.g., for swine, 21 C.F.R. § 558.128 (e)(3)(i), and for cattle *id.* § 558.128(e)(4)(xi)).
[123] Tetracycline (Chlortetracycline and Oxytetracycline)-Containing Premixes, 42 Fed. Reg. at 56266–67.
[124] *Id.*
[125] Emma Schwartz, *Inside an Early Attempt to Restrict Antibiotic Use on Farms*, PBS Frontline (Oct. 14, 2014), https://www.pbs.org/wgbh/frontline/article/inside-an-early-attempt-to-restrict-antibiotic-use-on-farms/; Amy Nordrum & Elizabeth Whitman, *Antibiotic Resistance: How Livestock Lobbyists and Drug Companies Hinder the US Fight Against Superbugs*, Int'l Bus. Times (Apr. 29, 2015), https://www.ibtimes.com/antibiotic-resistance-how-livestock-lobbyists-drug-companies-hinder-us-fight-against-1901499.
[126] *See* New Animal Drugs; Removal of Obsolete and Redundant Regulations, 68 Fed. Reg. 47272, 47274 (Aug. 8, 2003).
[127] *See* FDA, *2023 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals* tbl. 9a (2024), https://www.fda.gov/animal-veterinary/antimicrobial-resistance/2023-summary-report-antimicrobials-sold-or-distributed-use-food-producing-animals. Only approvals for the use of penicillin in animal *feed* have been withdrawn.
[128] J.M. Gilbert, *A Review of Studies Submitted to CVM Assessing the Effects of Sub-Therapeutic Use of Antimicrobial Drugs on the Salmonella Reservoir in Food Producing Animals* 2 (2001). Attached as Appendix B.
[129] *Id.* at 7.

Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals."[130] That year, FDA also issued a discussion paper, "A Proposed Framework for Evaluating and Assuring the Human Safety of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals," known as the Framework Document.[131]

In these documents FDA affirmed its authority to consider antibiotic resistance in its safety evaluation of animal drugs and extended this evaluation to all antibiotics used in food-producing animals, not just subtherapeutic uses in feed.[132] The Framework document also required pre-approval studies of resistance and pathogen shedding, on-farm post-approval monitoring with allowable thresholds for resistance, and reporting of sales data by drug makers.[133] While these 1999 documents represented a positive step in addressing antibiotic resistance, the Framework Document was unfortunately eviscerated before it could have any significant impact.

In 2003, in a new guidance document, GFI #152, FDA revised its approach for evaluating the safety of antimicrobial drugs during the new drug approval process. This guidance differed significantly from the previous approach laid out in regulations and the Framework Document. Rather than addressing the shortcomings of the previously required studies, the new guidance eliminated the requirement that drug sponsors submit data from studies on resistance or from pathogen shedding. In addition, unlike the Framework Document, GFI #152 does not include the concept of threshold monitoring or mention its application to previously approved drugs.

Instead GFI #152 lays out a qualitative risk assessment approach that uses available data to rank the risk based on the "potential for human health to be adversely impacted by the selection or emergence of antimicrobial resistant food-borne bacteria associated with the use of the drug in food-producing animals."[134] The risk assessment results in an estimation of the risk to human health from the proposed use with high, medium, and low risk as potential outcomes.

Despite FDA's obligation to ensure a "reasonable certainty of no harm," GFI #152 supports approval of drugs found to have high or medium risk under specific use restrictions.[135] The five specific use restrictions were (1) restriction on extent of use, (2) restriction of extra-label use, (3) review by advisory committee, (4) requirement for a veterinarian's order, and (5) monitoring post approval through the National Antimicrobial Resistance Monitoring System.[136]

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[130] Guidance for Industry: Consideration of the Human Health Impact of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals (GFI #78), 64 Fed. Reg. 70715, 70715 (Dec. 17, 1999).
[131] Discussion Paper: "A Proposed Framework for Evaluating and Assuring the Human Safety of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals," 64 Fed. Reg, 887, 887 (Jan. 6, 1999).
[132] New Animal Drugs; Removal of Obsolete and Redundant Regulations, 68 Fed. Reg. 47272, 47275.
[133] FDA, *A Proposed Framework for Evaluating and Assuring the Human Safety of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals* 16–17 (Aug. 14, 2003), https://www.regulations.gov/document/FDA-2003-N-0446-0008.
[134] Original GFI #152 at 20.
[135] *Id.* at 24.
[136] *Id.* at 22–23.

These five restrictions, even if used consistently and thoroughly and maintained to the present are not sufficiently stringent to move a drug with high-risk use to one where there is a "reasonable certainty of no harm."

4. In the Decades Since, FDA Has Backtracked on or Ignored Much of its Own Non-Binding Guidance.

In the decades since FDA issued GFI #152, FDA has inconsistently implemented the guidance, weak as it already was, and ultimately abandoned most of it.

For example, older antibiotics, like chlortetracyclin, have not been assessed under GFI #152, or if they have, the uses are inconsistent with the guidance recommendations with respect to duration. In 2004, FDA approved the withdrawal period for oxytetracycline being fed to cattle to be reduced down to zero days. Before allowing that change, FDA failed to require that the drugmaker first consider the impact of the change on antibiotic resistance. That is a significant omission since allowing the drug to be fed to cattle right up to the time of slaughter will almost certainly increase the probability that drug-resistant bacteria will be present at the time of slaughter, and as a result will contaminate the meat products being sold to consumers.[137]

Similarly, in 2006 and 2008, FDA allowed feeding pigs low doses of tylosin for disease control after they were given a high dose in feed or water, simply asserting (without evidence) that these changes "should not significantly impact public health; therefore, an evaluation of microbial food safety was not necessary at this time."[138] Indeed, FDA took these actions despite the fact that these approvals were for long-term use of an antibiotic ranked as critically important for human health and for use directly after the same drug had been administered in food and water—two factors likely to increase resistance risk.

In addition, FDA has often ignored the results of analyses required by GFI #152. Between 2001 and 2010, FDA reviewed the safety of 30 antibiotic animal feed additives previously approved, for a mix of growth-promotion and disease-prevention uses, applying the safety criteria in GFI #152 along with the criteria included in its 1973 regulation.[139] FDA concluded that 26 of the additives did not meet the 1973 safety criteria, and none of the additives would be approvable as new drugs under FDA's current guidelines.[140] Yet to date, FDA has not taken any action to

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[137] FDA, *Freedom of Information Summary: Supplemental New Animal Drug Application TM-50, TM-50D, TM-100, and TM-100D Type A Medicated Articles (oxytetracycline)*, at 6 (2004), https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/281 (establishing a "zero-day pre-slaughter withdrawal period for cattle treated with 10 mg oxytetracycline/lb body weight per day for 14 days").
[138] FDA, *Freedom of Information Summary: Supplemental New Animal Drug Application TYLAN 40, TYLAN 100, and TYLAN 100 Cal*, at 13 (2006), https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/290; FDA, *Freedom of Information Summary: Supplemental New Animal Drug Application TYLAN 40 and TYLAN 100*, at 11 (2008), https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/16485.
[139] *See* NRDC, *Playing Chicken with Antibiotics: Previously Undisclosed FDA Documents Show Antibiotic Feed Additives Don't Meet the Agency's Own Safety Standards* (2014), https://www.nrdc.org/sites/default/files/antibiotic-feed-fda-documents-IB.pdf.
[140] *Id.* at 7.

withdraw these approval for disease-prevention uses, instead only issuing guidance to phase out use for growth promotion.

Moreover, since 2003, FDA has removed three of the five already weak risk management tools that FDA put in place to mitigate human health risk from proposed antibiotic uses found to have high or medium risk of creating a human health problem.

1. **Extent of use restrictions**: Under the original 2003 GFI #152, high and medium risk uses of drugs should not be approved for high extent of use[141] —defined as any use in a group of animals for more than 21 days (as well as any herd- or flock-wide use).[142] In 2022, FDA proposed to remove the 21-day extent of use restriction, proposing instead that "[d]uration of use will be revised on a case-by-case basis in light of, but not limited to, animal species, disease risk period, and animal management husbandry practices, etc."[143] This revision would remove the reference to protecting human health and focus on animal needs, effectively eliminating use restrictions as a tool for making a high-risk drug "safe."

2. **Extra-label use restrictions**: FDA told members of the FDA Veterinary Medicine Advisory Committee (VMAC) in 2004[144] and 2006[145] that a finding of high risk during the risk assessment was not sufficient to put in place an extra-label use restriction on a proposed use of an animal drug even after an advisory committee vote to include these restrictions. FDA has never applied this restriction to a new animal drug in response to a review under GFI #152.

3. **Advisory committee review**: In 2013, review by advisory council was removed as an option when FDA disbanded the VMAC. Prior to this, only once did FDA not approve a

[141] Original GFI #152 at 25 tbl. 8.
[142] *Id.* at 23 tbl. 7. This is a longer duration than the 14 days used to trigger resistance studies previously under regulation.
[143] Draft GFI #152 at 20 tbl. 7; *see also* Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern; Revised Draft Guidance for Industry, 87 Fed. Reg. 77619, 77619 (Dec. 19, 2022).
[144] FDA, *Transcript – 2004 VMAC Meeting*, at 117–19 (2004), https://wayback.archive-it.org/7993/20170114023751/http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/VeterinaryMedicineAdvisoryCommittee/UCM127218.pdf.
[145] *Transcript – 2006 VMAC Meeting*, FDA (Sep. 25, 2006), https://wayback.archive-it.org/7993/20170114023717/http:/www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/VeterinaryMedicineAdvisoryCommittee/ucm126971.htm.

drug following the VMAC's recommendation against doing so.[146] Eliminating the VMAC eliminated the only path within GFI #152 for not approving a drug.[147]

The remaining two risk management tools employed by FDA under GFI #152 are essentially toothless:

1. **Veterinarian order**: In GFI #213 in 2017 and GFI #263 in 2023, FDA required a veterinarian's order for all MIAs.[148] While this would appear to be a positive step, it has unfortunately had the effect of eliminating any heightened scrutiny of high risk uses. Moreover, this veterinarian oversight is clearly inadequate to prevent dangerous resistance, given the fact of continuing overuse and resistance in animals (and the experience of overuse in human antibiotic use, almost all use of which in the U.S. is under doctor supervision).

2. **Post-approval monitoring**: FDA continues to monitor for resistance in bacteria collected from food-animals, meat, and sick humans. While positive, this oversight mechanism has been rendered toothless since there are no thresholds for action once resistance is detected. In fact, FDA rarely takes action and has only withdrawn approval of one use of an antibiotic in food-producing animals based on resistance—and even this withdrawal was initiated prior to GFI #152. (Moreover, of course, if resistance is found, then there is clearly already "harm," so this monitoring alone cannot meet the legal standard of safety.)

Essentially, over the last forty years, FDA has moved from requiring sponsors of drugs approved for use in food animals for over 14 days to submit tests showing that the drugs do not result in increased resistance nor result in increased shedding of pathogens, to a system where any antibiotic can be approved as long as it requires a veterinarian's order and has a duration of use shorter than 21 days. And now, FDA has proposed to remove the 21-day limit as well and broadened the definition of "therapeutic" use to include preventive uses.

During the same period resistance has increased and become a greater public health threat and the evidence of the risk from the overuse of antibiotics has also grown. Since the 1970s, the pathogens of concern have greatly expanded from *Salmonella* and *E. coli* to many others.[149]

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[146] In 2006, six of ten members of VMAC voted that the new animal drug cefquinome in animals had not been shown to be safe through the process of GFI #152. *Transcript – 2006 VMAC Meeting*, FDA (Sep. 25, 2006), https://wayback.archive-it.org/7993/20170114023717/http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/VeterinaryMedicineAdvisoryCommittee/ucm126971.htm. The drug was not subsequently approved. The comments of Dr. Sundlof, the Director of the Center for Veterinary Medicine at that time, with respect to this result are important. He stated the "companies did what they were asked to do [in regards to GFI #152], but the decision was still that it wasn't safe," suggesting that completing a risk assessment makes a drug safe, and that GFI #152 does not actually include an option to find a drug is unsafe. *Id.*

[147] Advisory Committee; Veterinary Medicine Advisory Committee; Termination, 78 Fed. Reg. 69991, 69991 (Nov. 22, 2013).

[148] *FDA Announces Implementation of GFI #213, Outlines Continuing Efforts to Address Antimicrobial Resistance*, FDA (Jan. 3, 2017), https://wayback.archive-it.org/7993/20190423131636/https://www.fda.gov/AnimalVeterinary/NewsEvents/CVMUpdates/ucm535154.htm.

[149] Ayidh M. Almansour et al., *The Silent Threat: Antimicrobial-Resistant Pathogens in Food-Producing Animals and Their Impact on Public Health*, 11 Microorganisms 2127 (2023).

FDA's regulatory approach has softened in direct opposition to the growth of the antibiotic resistance threat.

b. FDA's Guidance and Policies Continue to Allow the Use of Antibiotics for Disease Prevention and for Long Durations.

To understand how and why FDA's current policies and guidelines fail to prevent the overuse of antibiotics in animal agriculture today, it is important to understand a few key terms that appear in FDA guidance documents and use indications.

In GFI #213, issued in 2013 following the Natural Resources Defense Council petition and litigation, FDA contrasted "production uses" with "therapeutic uses" of antibiotics.[150] Production uses do not provide an animal health benefit and instead are intended to increase feed efficiency or promote growth, while therapeutic uses include uses for treatment, control, and prevention of specific diseases.

FDA defines "prevention" in GFI #209, issued in 2009:

> "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."

FDA in draft GFI #213 defines "disease treatment" and "disease control":

> Treatment: The drug is administered only to animals diagnosed (based on clinical signs or other appropriate diagnostic methods) with the indicated disease.
>
> Control: The drug is administered to a group of animals once a proportion of the animals in the group have been diagnosed (based on clinical signs or other appropriate diagnostic methods) with the indicated disease.

Critically, the distinction between uses for disease prevention and the other two types of uses FDA currently considers therapeutic (treatment and control) is that antibiotic uses for disease prevention are those for which there is no diagnosis of illness.

FDA's current guidance-based voluntary compliance program aims to curtail production uses of antibiotics in agriculture, leaving therapeutic (including disease prevention) uses—the vast majority of current uses—largely untouched. Extant guidance also does not require drug sponsors to limit the duration of use.

- In GFI #209, FDA summarized 40 years of evidence on the impact of antibiotic use in agriculture on antibiotic resistance. Based on these findings, it described two principles for "judicious use" of antibiotics in food animals: (1) the use of "medically important" antibiotics should be limited to uses "that are considered necessary for assuring animal

[150] Previously FDA regulation had contrasted subtherapeutic uses, defined as for production or disease prevention, with antibiotic use for disease treatment based on the human health impact of the use with subtherapeutic uses considered more dangerous.

health," and (2) veterinary oversight and consultation should be used in the use of antibiotic drugs.[151] GFI #209 thus discourages—but does not prohibit—the use of these antibiotics "to promote growth or improve feed efficiency" (that is, production uses), as injudicious but does not in any way limit disease prevention uses.[152]

- GFI #213 sets out a voluntary process for pharmaceutical companies to remove production uses (that is, growth-promotion and feed-efficiency uses) from product labels, and changes the use conditions of over-the-counter products to require veterinary oversight (either through a prescription or a veterinary feed directive).[153] It imposed no other limits on disease prevention uses.

- GFI #273 endorses disease prevention uses of MIAs and fails even to recommend a categorical limit on the duration of use for the MIAs the guidance addresses. The guidance states instead that there "are scenarios in which it will be necessary and consistent with the principles of judicious use to feed the drug for an extended period."[154]

Thus, as of today, FDA has taken no regulatory action to remove disease-prevention uses of antibiotics through its guidance, despite their never having been shown to be safe; and the agency has also failed to prevent the long duration use of many antibiotics.[155] As mentioned above, this regulatory approach, which sidesteps the requirement to initiate withdrawal proceedings for animal drugs not shown to be safe, is both arbitrary and capricious and contrary to law.

FDA's failure to act is especially glaring given that FDA itself has acknowledged that certain prevention uses "in the absence of any information that such animals were at risk of a specific disease" are injudicious.[156] Moreover, drawing a distinction between discouraged production uses (e.g., growth promotion) and permitted disease prevention uses makes little scientific or practical sense because the studies on which the recommendation not to use antibiotics for growth promotion are based either do not distinguish between types of use at all or when considering type of use look only at subtherapeutic antibiotic use, which includes both disease prevention and growth promotion.[157] In addition, in many cases the use of the antibiotic will be

[151] GFI #209 at 21–22.
[152] *Id.* at 21.
[153] GFI #213 at 6–7.
[154] GFI #273 at 7, 15.
[155] The lack of safety is particularly clear for the antibiotics that were part of the 1977 Notices of Opportunity of Hearing, and that consistently failed required safety tests with respect to the development of resistance. When FDA withdrew the Notices of Opportunity for Hearing, these uses did not then somehow become safe and likewise did not end. FDA's recommendation to add durations of use to these older antibiotics under GFI #273 will not make them safe.
[156] GFI #209 at 21–22. Misleadingly, GFI #209 also states that preventative uses may be judicious if "a veterinarian determines, based on the client's production practices and herd health history, that cattle being transported or otherwise stressed are more likely to develop a certain bacterial infection." *See id.* at 21. But such a use would be just as unsafe as any other preventative use insofar as it would contribute to the selection of resistant bacteria. And the use would be unnecessary as the disease risk described stems from stressful "production practices," which the client could alter instead of relying on antibiotics.
[157] *See*, *e.g.*, W. Q. Alali et al., *Longitudinal Study of Antimicrobial Resistance Among Escherichia Coli Isolates from Integrated Multisite Cohorts of Humans and Swine*, 74 Applied & Env't Microbiology 3672 (2008) (cited in GFI #209 at 15 and comparing swine workers with non-swine workers and not looking at specific antibiotic use);

identical for prevention and growth promotion with an identical dose administered for long durations to large numbers of animals.[158]

Looking beyond these guidance documents, in practice there are many extant FDA use indications that do not clearly state whether their intended purpose is for treatment or control or use the term control inconsistently with the current definition of control.[159]A close examination of several of these ambiguous use indications reveals that they are in fact prevention uses. For example, FDA allows the use of lincomycin to control swine dysentery "on premises with a history of swine dysentery but where symptoms have not yet occurred."[160] Other indications allow use for "reduction of [] incidence" of an anticipated problem which is not linked to diagnosis of illness.[161] There are also uses for "maintenance of weight gains" which is a type of production use even though targeted for animals that are sick.[162]

For this petition, we consider as "preventive uses" all these indications that are not based on diagnosis of illness as well as uses for "maintenance of weight gains" not aimed at treating or controlling disease. In Appendix A, Petitioners list indications that we have identified as for disease prevention along with those with long durations independent of reason of use.

c. Current Routine Use of Medically Important Antibiotics in Animals Remains Extremely High.

The failure of FDA's voluntary compliance program is evident from the continued extensive use of antibiotics in agriculture. Considering only MIAs—that is, drugs in antibiotic classes used in human medicine—more than twice as many of the antibiotics sold are used to raise food animals (6 million kilograms of active ingredient) as are used to treat sick humans (2.67 million

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T.W. Alexander et al., *Effect of Subtherapeutic Administration of Antibiotics on the Prevalence of Antibiotic-Resistant Escherichia Coli Bacteria in Feedlot Cattle*, 74 Applied & Env't Microbiology 4405 (2008); Ranjana Sharma et al., *Diversity and Distribution of Commensal Fecal Escherichia coli Bacteria in Beef Cattle Administered Selected Subtherapeutic Antimicrobials in a Feedlot Setting*, Applied & Env't Microbiology 6178 (2008) (cited in GFI #209 at 15 and referring to "subtherapeutic" use, but the antibiotics shown to select for resistance—chlortetracycline and sulfamethazine—are still approved for disease prevention at the same dose today as that used in the studies).

[158] The likelihood of overuse is increased because many of the preventive use dosages overlap with previous approvals for growth promotion and feed efficiency, indicating there is an economic benefit to using antibiotics for disease prevention. *See* Pew Charitable Trusts, *Gaps in FDA's Antibiotics Policy: Many Drugs May Still Be Available for Food Animals at Growth-Promotion Levels* 1 (2014), https://www.pew.org/-/media/assets/2014/11/hhif_fda213gaps_v4.pdf ("Many drugs may still be available for food animals at growth-promotion levels."). *See* Appendix A column labeled "Growth Dose," which indicates where the current prevention approvals overlap with the growth promotion dose.

[159] This not surprising since FDA did not define control until a concept paper on defining durations of use in 2021—long after these control uses were approved. *See* FDA, *Potential Approach for Defining Durations of Use for Medically Important Antimicrobial Drugs Intended for Use in or on Feed: A Concept Paper* (Jan. 24, 2021), https://www.regulations.gov/document/FDA-2016-D-2635-0269.

[160] 21 C.F.R. § 558.325(e)(2)(i) (2025).

[161] *See*, *e.g.*, *id.* § 558.128(e)(4)(ii) (2025), which is an approval for the use of the antibiotic chlortetracycline. "For reduction of the incidence of liver abscesses" in feedlot cattle. *Id.* This approval like many for "reduction of [] incidence" has no duration limit, meaning it can be used during the whole period the animal is on feed.

[162] *See*, *e.g.*, *id.* § 558.140(e)(2), which is an approval for the use of the combination of chlortetracycline and sulfamethazine in the feed of pigs for "maintenance of weight gains in the presence of atrophic rhinitis," along with other indications for treatment, prevention, and reduction of incidence. These indications have no duration limit.

kilograms).[163] Most of the MIAs sold for use in food-producing animals are administered to groups of animals through feed (65%) or water (30%).[164] The bulk of MIAs in food-producing animals goes to swine and cattle, with over 40% of sales by weight going to each of these two livestock sectors.[165] Turkeys receive another 11% of MIAs, while only 4% of MIAs sold for use in food-producing animals are for chickens.[166] 18 times more antibiotics is sold for use in swine than in chicken per kilogram of the respective animals' body weights.[167] Sales for cattle are approximately 7 times more than for chicken.[168]

Since 2017, sales of MIAs for use in food-producing animals has increased by 28% overall with a 50% increase in pigs, a 25% increase in cattle, and 11% increase in turkeys.[169] While sales of MIAs for use in chicken are still slightly lower than in 2017, they increased by almost 80% in 2024 when compared to 2023.[170] This large rise in sales in 2024 indicates that voluntary reductions in use of antibiotics by livestock and poultry producers can rapidly be eroded, supporting the need for more effective government action.

Moreover, in addition to MIAs, an additional 4 to 5 million kilograms of antibiotics that are not in classes used in human medicine are also sold for use in food-producing animals each year.[171] As explained further below, the overuse of these non-MIA's also presents risks to public health.

d. Data Suggests that Antibiotics in Agriculture Are Mostly Used for Prevention, Not Treatment.

Antibiotics for disease prevention are "massively overused" and "not uncommonly as a crutch to compensate for poor management or husbandry practices that increase the risk of disease."[172] In

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[163] David Wallinga, *Antibiotic Use Remains Far Too Intensive in U.S. Livestock: By Contrast, Falling Rates of Medical Use Suggest More Effective Stewardship*, NRDC (Sep. 11, 2023), https://www.nrdc.org/bio/david-wallinga-md/antibiotic-use-remains-far-too-intensive-us-livestock.

[164] *See* FDA, *2024 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals* tbl. 6b (2025), https://www.fda.gov/animal-veterinary/antimicrobial-resistance/2024-summary-report-antimicrobials-sold-or-distributed-use-food-producing-animals.

[165] *Id.* at tbl. 4a.

[166] *Id.*

[167] *Biomass-Adjusted Antimicrobial Sales and Distribution Data in Food Producing Animals: Interactive Summary*, FDA, https://www.fda.gov/animal-veterinary/antimicrobial-resistance/biomass-adjusted-antimicrobial-sales-and-distribution-data-food-producing-animals-interactive (last updated Dec. 5, 2025).

[168] *Id.*

[169] *See* FDA, *2024 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals* tbl. 4b (2025), https://www.fda.gov/animal-veterinary/antimicrobial-resistance/2024-summary-report-antimicrobials-sold-or-distributed-use-food-producing-animals.

[170] *Id.*

[171] *See id*. at tbl. 2b.

[172] Scott Weese, *Antimicrobial Prophylaxis in Animals*, Worms & Germs Blog (Nov. 20, 2023), https://www.wormsandgermsblog.com/2023/11/articles/miscellaneous/antimicrobial-prophylaxis-in-animals/. Dr. Weese is the Director of the Centre for Public Health and Zoonosis the University of Guelph 's Ontario Veterinary College and the former Canada Research Chair in Zoonotic Diseases. He is a veterinary internal medicine specialist and the chief of infection control at the Ontario Veterinary College. He is an expert in infectious and parasitic animal disease, including rabies, tick-borne diseases, antimicrobial resistance and emerging diseases. A review of preventive use of antibiotics for prevention of bovine respiratory disease similarly found, "[d]espite widespread use of prevention products, the need for antimicrobial mass medications should be re-evaluated since the underlying problem is more likely the segmented infrastructure of the feedlot and veal calf industries compared to the disease

fact, reliable data from numerous studies strongly indicate that the majority of animal antibiotic use is for disease prevention, not control or treatment.[173] Data collected by federal agencies do not contradict these studies. Rather, the federal government has failed to monitor and parse the degree to which antibiotics in agriculture are presently being used for prevention rather than treatment. For example, the national sales data that FDA collects are based on drug makers' reporting the amount of antibiotic active ingredient distributed or sold. Given that an active ingredient often has many indications, it is generally impossible to determine reason of use from FDA sales data. Also, USDA periodically surveys livestock and poultry producers about their antibiotic use. The only recent survey that provides information on types of use for swine, conducted in 2021, shows that the most common reason for use of antibiotics in the feed of growing herds was for "disease prevention and control,"[174] and does not distinguish between control and prevention. Similarly, the most recent report including data on reason of use for feedlot cattle by USDA, with data collected in 2016, only distinguished between type of illness (e.g., respiratory disease or diarrhea), not whether the use was for treatment, control, or prevention. This study did find though that the feed antibiotic given most frequently to cattle is tylosin, which in cattle is only approved for "reduction of the incidence of liver abscesses," which is a prevention-type use, and is thus consistent with other studies finding that use in food animals is most often for disease prevention.[175]

As will be explained further below, FDA must withdraw approval for such disease prevention uses to protect public health. Better stewardship is possible and has been achieved in many European countries where overall volume of antibiotics sold per kilogram of livestock raised is vastly lower than in the US.[176] Indeed, many years ago several major livestock producing countries in Europe discovered that ending the use of antibiotics in animals without diagnosed disease was an essential step to curbing the overuse of these drugs.[177]

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itself." Keith E. Baptiste & Niels C. Kyvsgaard, *Do Antimicrobial Mass Medications Work? A Systematic Review and Meta-Analysis of Randomised Clinical Trials Investigating Antimicrobial Prophylaxis or Metaphylaxis Against Naturally Occurring Bovine Respiratory Disease*, 75 Pathogens & Disease (2017). Though it should be noted that use in animals may be justified for individual prophylaxis in limited high risk situations such as surgery.

[173] *See* Katie J. Hope et al., *Antimicrobial Use in 22 U.S. Beef Feedyards: 2016–2017*, 67 Zoonoses & Pub. Health 94, 100 tbl. 5 (2020) (finding in-feed macrolides the most frequently used); Stephanie C. Rutten-Ramos et al., *Population-Level Analysis of Antibiotic Use and Death Rates in Beef Feedlots over Ten Years in Three Cattle-Feeding Regions of the United States*, 259 J. Am. Veterinary Med. Ass'n 1344 (2021).

[174] USDA, *Swine Part II: NAHMS 2021 – Reference of Management Practices on Large-Enterprise Swine Operations in the United States* tbls. C.5.f, D.5.f, E.5.f., F.5.f (2023), https://www.aphis.usda.gov/livestock-poultry-disease/nahms/swine/swine-2021-part-ii-reference-management-practices-large.

[175] USDA, *Antimicrobial Use and Stewardship on U.S. Feedlots, 2017*, at 16 (2019), https://www.aphis.usda.gov/sites/default/files/amu-feedlots_1.pdf; for the approved indication in cattle for tylosin, see 21 C.F.R. § 558.625 (e)(2)(vi).

[176] NRDC, *U.S. Livestock Industries Persist in High-Intensity Antibiotic Use: Curbing Overuse Is Critical to Slow the Spread of Antibiotic Resistance* (2022), https://www.nrdc.org/sites/default/files/us-livestock-industries-persist-high-intensity-antibiotic-use-ib.pdf.

[177] *Id*.

VI. SCIENCE IS CLEAR THAT THE ROUTINE USE OF MEDICALLY IMPORTANT ANTIBIOTICS IN ANIMAL FEED OR WATER FOR PREVENTATIVE USES IS NOT SAFE BECAUSE FDA CANNOT ESTABLISH A REASONABLE CERTAINTY OF NO HARM

Over 40 years of studies have consistently shown that the use of antibiotics in food-producing animals leads to the selection of resistant bacteria in and on food animals and that these resistant bacteria can be transferred to humans through direct contact with the animals, through food, and indirectly through contamination of the environment. These resistant bacteria can directly cause infections in humans that are more difficult to treat than susceptible bacteria; and if these bacteria do not directly cause illness to humans, the bacteria can transfer resistance genes to other bacteria that cause illness, making those other bacteria more difficult to treat. The following subsections provide a summary of the undisputed science.

a. The Core Science of How Antibiotic Use Creates Antibiotic Resistance Is Beyond Dispute.

1. All Antibiotic Use Can Drive Resistance.

All uses of antibiotics can increase,[178] or drive, antibiotic resistance, whether that use occurs in humans, animals, or plants.[179] This is supported by culture-based studies,[180] studies in laboratory animals,[181] studies in human patients,[182] studies in food-producing animals,[183] and studies comparing use and resistance between farms[184] and countries.[185]

The foundational science of antibiotic resistance has been acknowledged for decades. Natural antibiotics have existed for billions of years, and undoubtedly so have bacteria carrying

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[178] Thomas F. O'Brien, *Emergence, Spread, and Environmental Effect of Antimicrobial Resistance: How Use of an Antimicrobial Anywhere Can Increase Resistance to Any Antimicrobial Anywhere Else*, 34 Clinical Infectious Diseases S78 (2002).

[179] CDC, *Antibiotic Resistance Threats in the United States, 2013*, at 11 (2013), https://www.cdc.gov/antimicrobial-resistance/media/pdfs/ar-threats-2013-508.pdf?CDC_AAref_Val=https://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf ("The use of antibiotics is the single most important factor leading to antibiotic resistance around the world."); *see also* Patrick Munk et al., *The European Livestock Resistome*, 9 Microbial Ecology (2024); Frank M. Aarestrup, *The Livestock Reservoir for Antimicrobial Resistance: A Personal View on Changing Patterns of Risks, Effects of Interventions and the Way Forward*, 370 Phil. Transactions Royal Soc'y Bull. (2015); Frank M. Aarestrup & Henrik C. Wegener, *The Effects of Antibiotic Usage in Food Animals on the Development of Antimicrobial Resistance of Importance for Humans in Campylobacter and Escherichia Coli*, 1 Microbes Infect 639 (1999); H. Williams Smith, *The Effect of the Use of Antibacterial Drugs, Particularly as Food Additives, on the Emergence of Drug-Resistant Strains of Bacteria in Animals*, 15 New Zealand Veterinary J. 153 (1967); Sally A. Miller, Jorge Pinto Ferreira & Jefffrey T. Le Jeune, *Antimicrobial Use and Resistance in Plant Agriculture: A One Health Perspective*, 12 Agric. (2022); Tarequl Islam et al., *Antibiotic Resistance in Plant Pathogenic Bacteria: Recent Data and Environmental Impact of Unchecked Use and the Potential of Biocontrol Agents as an Eco-Friendly Alternative*, 13 Plants (2024).

[180] Karl Drlica, *The Mutant Selection Window and Antimicrobial Resistance*, 52 J. Antimicrobial Chemotherapy 11 (2003); L.Y. Fuchs et al., *In-Vitro Selection of Fluoroquinolone Resistance in Salmonella Typhimurium*, 32 J. Antimicrobial Chemotherapy 171 (1993); Joanna Krajewska, Stefan Tyski & Agnieszka E. Laudy, *In Vitro Resistance-Predicting Studies and In Vitro Resistance-Related Parameters—A Hit-to-Lead Perspective*, 17 Pharmaceuticals 1068 (2024); Marta Lukačišinova, Booshini Fernando & Tobias Bollenbach, *Highly Parallel Lab Evolution Reveals that Epistasis Can Curb the Evolution of Antibiotic Resistance*, 11 Nature Commc'ns (2020); Tom Vogwill et al., *Testing the Role of Genetic Background in Parallel Evolution Using the Comparative Experimental Evolution of Antibiotic Resistance*, 31 Molecular Biology & Evolution 3314 (2014).

[181] Zina Gestels et al., *'Acceptable' Concentrations of Enrofloxacin in Food Lead to Reduced Enrofloxacin Susceptibility in a Mouse Model of Gastrointestinal Klebsiella Pneumoniae*, 13 Microbiology Spectrum (2025); Hongyuhang Ni et al., *Exposure to the Growth Promoter Tylosin Elicits Gut Microbiota Disruption and Metabolic Imbalance in Mouse Model*, 202 Env't Int'l (2025); Ce Huang et al., *Effects of Four Antibiotics on the Diversity of the Intestinal Microbiota*, 10 Microbiology Spectrum (2022); Camilla Lester, Niels Frimodt-Møller & Anette M. Hammerum, *Conjugal Transfer of Aminoglycoside and Macrolide Resistance Between Enterococcus faecium Isolates in the Intestine of Streptomycin-Treated Mice*, 235 FEMS Microbiology Letters 385 (2004).

[182] Sang-Ho Choi et al., *Emergence of Antibiotic Resistance During Therapy for Infections Caused by Enterobacteriaceae Producing AmpC β-Lactamase: Implications for Antibiotic Use*, 52 Antimicrobial Agents & Chemotherapy 995 (2007); D.L. Dworzack et al., *Emergence of Resistance in Gram-Negative Bacteria During Therapy with Expanded-Spectrum Cephalosporins*, 6 Eur. J. Clinical Microbiology 456 (1987); J.E. McGowan Jr., *Antimicrobial Resistance in Hospital Organisms and Its Relation to Antibiotic Use*, 5 Revs. Infectious Diseases 1033 (1983); Mathew Stracy et al., *Minimizing Treatment-Induced Emergence of Antibiotic Resistance in Bacterial Infections*, 375 Sci. 889 (2022); Jennifer K. Thomas et al., *Pharmacodynamic Evaluation of Factors Associated with*

resistance to those antibiotics.[186] Man-made antibiotics have existed for roughly one hundred years.

Exposing bacterial populations to antibiotics can kill off the bacteria lacking resistance traits, while resistant strains survive and multiply, passing genes conferring that resistance onto their offspring.[187] This sequence of events explains how over time, the ongoing presence of antibiotics—whether put there by nature or by man—"selects for" the spread of antibiotic resistance, both resistant bacteria and resistance genes. What has changed with the introduction of human made antibiotics is a large increase in the number of bacteria with large plasmids containing multiple resistance genes along with increased ability to share genes conferring resistance between them.[188] As a result, bacterial populations—both locally and globally—contain increasingly higher proportions of antibiotic-resistant strains, and individual bacteria are resistant to a growing number of antibiotics.[189]

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the Development of Bacterial Resistance in Acutely Ill Patients During Therapy, 42 Antimicrobial Agents & Chemotherapy 521 (1998).

[183] T.W. Alexander et al., *Effect of Subtherapeutic Administration of Antibiotics on the Prevalence of Antibiotic-Resistant Escherichia coli Bacteria in Feedlot Cattle*, 74 Applied & Env't Microbiology 4405 (2008); Jonathan Bastard et al., *Drivers of ESBL-Producing Escherichia coli Dynamics in Calf Fattening Farms: A Modelling Study*, 12 One Health (2021); Elke Burow et al., *Antibiotic Resistance in Escherichia coli from Pigs from Birth to Slaughter and Its Association with Antibiotic Treatment*, 165 Preventive Veterinary Med. 52 (2019); Neena Kanwar et al., *Impact of Treatment Strategies on Cephalosporin and Tetracycline Resistance Gene Quantities in the Bovine Fecal Metagenome,* 4 Sci. Reps. (2014); Bruce E. Langlois et al., *Antibiotic Resistance in Pigs Following a 13 Year Ban*, 62 J. Animal Sci. 18 (1986); Hayden E. Williams et al., *Effects of Chlortetracycline Alone or in Combination with Direct Fed Microbials on Nursery Pig Growth Performance and Antimicrobial Resistance of Fecal Escherichia coli*, 96 J. Animal Sci. 5166 (2018); Fangzhou Wu et al., *Effects of Tylosin Administration Routes on the Prevalence of Antimicrobial Resistance Among Fecal Enterococci of Finishing Swine*, 16 Foodborne Pathogens & Disease 309 (2019).

[184] Pablo Rovira et al., *Characterization of the Microbial Resistome in Conventional and 'Raised Without Antibiotics' Beef and Dairy Production Systems*, 10 Frontiers in Microbiology (2019); Kenji Sato, Paul C. Bartlett & Mahdi A. Saeed, *Antimicrobial Susceptibility of Escherichia coli Isolates from Dairy Farms Using Organic Versus Conventional Production Methods*, 266 J. Am. Veterinary Med. Ass'n 589 (2005); Tara C. Smith et al., *Methicillin-Resistant Staphylococcus aureus in Pigs and Farm Workers on Conventional and Antibiotic-Free Swine Farms in the USA*, 8 PLOS ONE (2013); Amit Vikram et al., *Impact of 'Raised Without Antibiotics' Beef Cattle Production Practices on Occurrences of Antimicrobial Resistance*, 83 Applied & Env't Microbiology (2017).

[185] Ilias Chantziaras et al., *Correlation Between Veterinary Antimicrobial Use and Antimicrobial Resistance in Food-Producing Animals: A Report on Seven Countries*, 69 J. Antimicrobial Chemotherapy 827 (2014); Milan Čižman, *The Use and Resistance to Antibiotics in the Community*, 21 Int'l J. Antimicrobial Agents 297 (2003); Eur. Ctr. Disease Prevention & Control, Eur. Food Safety Auth., & Eur. Meds. Agency, *Antimicrobial Consumption and Resistance in Bacteria from Humans and Food-Producing Animals: Fourth Joint Inter-Agency Report on Integrated Analysis of Antimicrobial Agent Consumption and Occurrence of Antimicrobial Resistance in Bacteria from Humans and Food-Producing Animals in the EU/EEA JIACRA IV – 2019−2021*, 22 Eur. Food Safety Auth. J. (2024).

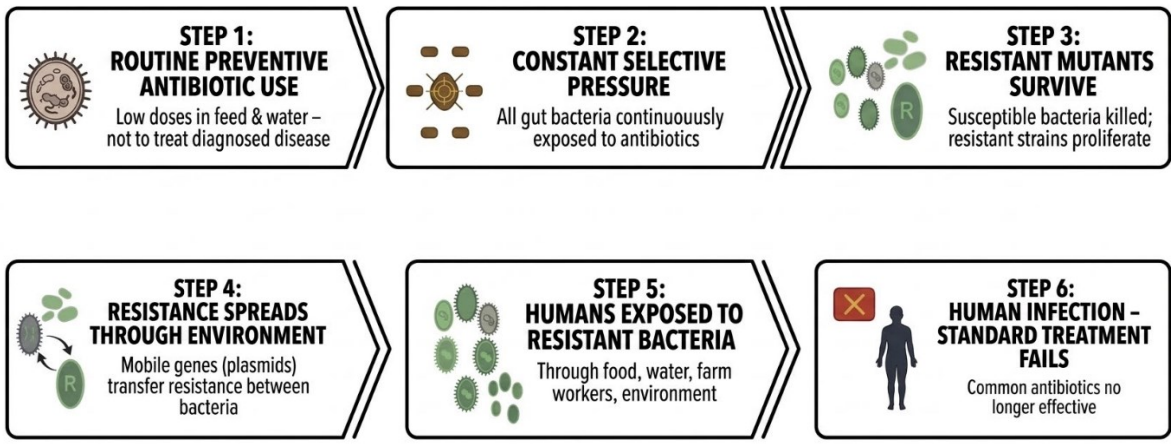
[186] Gerard D. Wright & Hendrik Poinar, *Antibiotic Resistance Is Ancient: Implications for Drug Discovery*, 20 Trends Microbiology 157 (2012); Christian J.H. von Wittensdorf et al., *Dissemination of Antimicrobial Resistance in Microbial Ecosystems Through Horizontal Gene Transfer*, 7 Frontiers Microbiology (2016).

[187] *Antibiotic Resistance*, MedlinePlus, https://medlineplus.gov/antibioticresistance.html (last updated Sep. 27, 2024).

[188] Adrian Cazeras et al., *Pre- and Postantibiotic Epoch: The Historical Spread of Antimicrobial Resistance*, 390 Sci. (2025); *supra* note 58.

[189] Dae-Wi Kim & Chang-Jun Cha, *Antibiotic Resistome from the One-Health Perspective: Understanding and Controlling Antimicrobial Resistance Transmission*, 53 Experimental & Molecular Med. 301 (2021); Kihyun Lee et

Figure 9. How Antibiotic Resistance Develops: From Livestock Antibiotic Use to Human Harm[190]



Even the overuse of non-MIA antibiotics can contribute to this public health problem. Non-MIAs can still contribute to resistance to medically important drugs through the process of co-selection.[191] Indeed, new evidence has confirmed that the use of one antibiotic may select for resistance to multiple antibiotics. A study of the effects of antibiotics on the intestinal microbes of pigs, for example, found that intestinal bacteria exposed to an antibiotics cocktail acquired resistance not only to antibiotics in the cocktail (such as penicillin) but also to other antibiotics (such as aminoglycoside).[192]

In accepting his 1945 Nobel Prize for discovering penicillin, Alexander Fleming warned of the danger of bacteria made resistant to treatment by the misuse antibiotics.[193] The next year, Joshua Lederberg and Edward Tatum demonstrated that bacteria could share genes[194] through multiple

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al, *Population-Level Impacts of Antibiotic Usage on the Human Gut Microbiome*, 14 Nature Communications 1 (2023); Andrea Marino et al., *The Global Burden of Multidrug-Resistant Bacteria*, 6 Epidemiologia 21 (2025); Bintao Li et al., *Global Health Risks Lurking in Livestock Resistome*, 11 Sci. Advances (2025).

[190] This figure depicts the mechanism by which routine administration of low-dose antibiotics to entire herds through feed and water generates antibiotic-resistant bacteria that ultimately cause human illness and death. Resistant bacteria circulate back through the herd continuously, compounding resistance pressure with each cycle before any human exposure occurs.

CDC, *Antibiotic Resistance Threats in the United States 2019* (2019), https://www.cdc.gov/antimicrobial-resistance/data-research/threats/index.html; WHO*, Antimicrobial Resistance: Global Report on Surveillance* (2014), https://iris.who.int/server/api/core/bitstreams/43e22b21-7ea9-4795-a226-d34513c2c39e/content; FDA, *2023 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals* (2024), https://www.fda.gov/animal-veterinary/antimicrobial-resistance/2023-summary-report-antimicrobials-sold-or-distributed-use-food-producing-animals; Claas Kirchhelle, *Pharming Animals: A Global History of Antibiotics in Food Production (1935-2017)*, 4 Palgrave Comm'cns (2018).

[191] Asalia Ibrahim, Jason Au & Alex Wong, *Ionophore Resistance Genes Are Geographically Widespread and Linked to Resistance to Medically Important Antibiotics*, 10 Antimicrobial Chemotherapy (2025).

[192] Torey Looft et al., *Bacteria, Phages and Pigs: The Effects of In-Feed Antibiotics on the Microbiome at Different Gut Locations*, 8 Int'l Soc'y Microbial Ecology J. 1566, 1574 (2014).

[193] *Sir Alexander Fleming – Nobel Prize Lecture*, The Nobel Prize, https://www.nobelprize.org/prizes/medicine/1945/fleming/lecture/ (last visited Mar. 31, 2026).

[194] *Joshua Lederberg – Facts*, The Nobel Prize, https://www.nobelprize.org/prizes/medicine/1958/lederberg/facts/ (last visited Mar. 31, 2026).

processes which we now know can spread multiple, physically linked antibiotic resistance genes.[195]

With each passing year, scientists uncover more details that enhance understanding of how the use and overuse of antibiotics continue to spread antibiotic resistance. But the core science largely remains the same. The directionality of the resistance problem also does not change. It continues to worsen at an "alarming, and accelerating rate."[196] As resistance increases in bacterial populations, more antibiotic treatments will fail,[197] infections will persist for longer, and treatment costs will rise, as will deaths.[198]

2. Since Antibiotic Resistance Is Gene-Based, It Can Move Very Swiftly and Far.

Resistance involves genetic changes in bacteria. Most bacteria reproduce by dividing every few hours, during which spontaneous mutations in the genetic code can arise. Some gene mutations can help bacteria survive exposure to antibiotics. Bacteria can also mutate in response to stress, including exposure to antibiotics.[199] Resistance may begin at a low level, enabling bacteria to survive minimal antibiotic exposure; with repeated exposure, they can acquire additional mutations that confer resistance to higher drug concentrations. These resistant bacteria can then reproduce and spread, especially in an environment of continued antibiotic exposure. Resistance can be multiplied and spread clonally, meaning thorough reproduction and distribution of bacteria containing resistance genes. Ongoing exposure to antibiotics can select for compensatory mutations that reduce the fitness cost of resistance, thereby enabling resistant bacteria to persist even in the absence of exposure to the antibiotic.[200] The end result of high-level antibiotic use is the clonal spread regionally and globally within human and animal populations of strains of multidrug-resistant bacteria, including pathogenic bacteria.[201]

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[195] Zheng Jie Lian et al., *Convergence of Plasmid-Driven Virulence and Antibiotic Resistance in Escherichia coli*, 17 Nature Commc'n (2025).

[196] Nat'l Inst. of Allergy & Infectious Diseases, *NIAID's Antibiotic Resistance Research Framework: Current Status and Future Directions* 2 (2019) [hereinafter 2019 NIAID Report] https://www.niaid.nih.gov/sites/default/files/AR2019.pdf, (discussing "The Evolution and Accelerating Pace of Antibiotic Resistance"); Gang Liu, Line Elnif Thomsen & John Elmerdahl Olsen, *Antimicrobial-Induced Horizontal Transfer of Antimicrobial Resistance Genes in Bacteria: A Mini-Review*, 77 J. Antimicrobial Chemotherapy 556 (2022).

[197] *See* Calvin M. Kunin, *Resistance to Antimicrobial Drugs: A Worldwide Calamity*, 118 Annals Internal Med. 557 (1993).

[198] Nat'l Acads. of Scis., Engineering & Med., Health & Med. Div., Bd. Population Health & Pub. Health Practice, Comm. Long-Term Health & Econ. Effects of Antimicrobial Resistance in the U.S., *Chapter 3, The Health and Economic Burden of Resistance*, *in Combating Antimicrobial Resistance and Protecting the Miracle of Modern Medicine* (Guy H. Palmer & Gillian J. Buckley eds., 2021).

[199] J.L. Martinez & F. Baquero, *Mutation Frequencies and Antibiotic Resistance*, 44 Antimicrobial Agents & Chemotherapy 1771 (2000).

[200] Pia Schulz zur Wiesch, Jan Engelstädter & Sebastian Bonhoeffer, *Compensation of Fitness Costs and Reversibility of Antibiotic Resistance Mutations*, 54 Antimicrobial Agents & Chemotherapy 2085 (2010); Ankita Pal & Dan I. Andersson, *Bacteria Can Compensate the Fitness Costs of Amplified Resistance Genes via a Bypass Mechanism*, 15 Nature Commc'ns 1 (2024).

[201] Patrick Butaye et al., *The Clonal Spread of Multidrug-Resistant Non-Typhi Salmonella Serotypes*, 8 Microbes & Infection 1891 (2006); Daniel F.M. Monte et al., *Clonal Spread of blaCTX-M-65 Producing Salmonella enterica Serovars Detected in Poultry Retail Meat in North Carolina, USA*, 15 Sci. Reps. 1 (2025); Orhan Sahin et al., *Molecular Evidence for Zoonotic Transmission of an Emergent, Highly Pathogenic Campylobacter jejuni Clone in*

In addition to mutation and subsequent clonal spread, bacteria can acquire genetic material, such as small packets of DNA called plasmids, from other bacteria through horizontal gene transfer (HGT). HGT is the bacterial process most responsible for the widespread proliferation of antibiotic resistance observed today.[202] Studies have shown that exposure to antibiotics may increase the rate at which bacteria transfer resistance genes to other bacteria. An experiment in pigs found an increase in transfers of mobile genetic material from resistant bacterial strains to susceptible strains in the presence of low doses of certain antibiotics. Some of these transfers occurred between different species of bacteria.[203] Mobile genetic elements (MGEs) specialize in moving DNA around the bacterial genome and are the crucial mediators of HGT. They can aggregate multiple genes within a single transmissible packet, along with other DNA fragments which function to facilitate more rapid movement of these genes and other genetic elements among different bacterial populations.[204] For example, plasmids often contain multiple, physically-linked antibiotic resistance genes. [205] Exposing bacterial populations to a single antibiotic can select for the spread of strains carrying one of these plasmids in a process called co-selection.[206] Doing so increases the prevalence of all forms of antibiotic resistance represented on that plasmid, not simply resistance to the antibiotic being used.[207] In addition to multiple antibiotic resistance genes, virulence genes can also be simultaneously transmitted via HGT, enhancing a pathogen's ability to cause disease while simultaneously complicating treatment.[208] MGE-facilitated transfers of resistance genes can occur between members of different species of bacteria,[209] and strains of bacteria that do not normally cause illness can act as a reserve of resistance genes that can be transferred to disease-causing bacteria, making them even more dangerous.[210]

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the United States, 50 J. Clinical Microbiology 680 (2012); Abdeljallil Zeggay et al., *Genome Analysis of Methicillin-Resistant and Methicillin-Susceptible Staphylococcus aureus ST398 Strains Isolated from Patients with Invasive Infection*, 11 Microorganisms 1446 (2023).

[202] Christian J.H. von Wittensdorf et al., *Dissemination of Antimicrobial Resistance in Microbial Ecosystems Through Horizontal Gene Transfer*, 7 Frontiers Microbiology (2016).

[203] Matt T. Brewer et al., *Effects of Subtherapeutic Concentrations of Antimicrobials on Gene Acquisition Events in Yersinia, Proteus, Shigella, and Salmonella Recipient Organisms in Isolated Ligated Intestinal Loops of Swine*, 74 Am. J. Veterinary Rsch. 1078 (2013).

[204] Salvador Castañeda-Barba, Eva M. Top & Thibault Stalder, *Plasmids, a Molecular Cornerstone of Antimicrobial Resistance in the One Health Era*, 22 Nat. Revs. Microbiology 18 (2024); Sally R. Partridge et al., *Mobile Genetic Elements Associated with Antimicrobial Resistance*, 31 Clinical Microbiology Revs. (2018).

[205] Alessandra Carattoli, *Plasmids and the Spread of Resistance*, 303 Int'l J. Med. Microbiology 298 (2013).

[206] *Id.*

[207] Jiratchaya Puangseree et al., *Molecular Basis of the Persistence of Chloramphenicol Resistance Among Escherichia coli and Salmonella spp. from Pigs, Pork and Humans in Thailand*, 19 PLOS ONE (2024).

[208] Yiqin Deng et al., *Horizontal Gene Transfer Contributes to Virulence and Antibiotic Resistance of Vibrio harveyi 345 Based on Complete Genome Sequence Analysis*, 20 BMC Genomics (2019); Bijay K. Khajanchi & Steven L. Foley, *Antimicrobial Resistance and Increased Virulence of Salmonella*, 10 Microorganisms (2022); Sima Yaron et al., *Vesicle-Mediated Transfer of Virulence Genes from Escherichia coli O157:H7 to Other Enteric Bacteria*, 66 Applied & Env't Microbiology 4414 (2000).

[209] Marcos Parras-Moltó et al., *The Transfer of Antibiotic Resistance Genes Between Evolutionarily Distant Bacteria*, 10 mSphere (2025).

[210] D.P. Blake et al., *Transfer of Antibiotic Resistance Between Commensal and Pathogenic Members of the Enterobacteriaceae Under Ileal Conditions*, 95 J. Applied Microbiology 428 (2003); Samuel C. Forster et al., *Strain-Level Characterization of Broad Host Range Mobile Genetic Elements Transferring Antibiotic Resistance from the Human Microbiome*, 13 Nature Commc'ns (2022); Ross S. McInnes et al., *Horizontal Transfer of Antibiotic Resistance Genes in the Human Gut Microbiome*, 53 Current Op. Microbiology 35 (2020).

In summary, over the past few decades, the increased use of antibiotics has dramatically accelerated the rate at which horizontal transfer is occurring,[211] while hugely increasing the number of antibiotic-resistant strains of bacteria.[212] And new evidence continues to accumulate demonstrating as much. Two more recent examples of such studies include:

- In a review from 2022 analyzing antimicrobial-induced horizontal transfer of antimicrobial resistance genes, researchers Liu et al. concluded that antimicrobial treatment may lead to up-regulation of the genes encoding the transfer machinery involved in conjugation transfer, and that this leads to an increased number of transfer events.[213] Bacterial interactions fundamentally facilitate the propagation of drug resistance, and extracellular vesicles play a critical role in interbacterial communication.
- A 2025 study by Li and colleagues found that certain drug-resistant *E. coli* bacteria release tiny particles called outer membrane vesicles (OMVs). These particles carry a resistance enzyme known as NDM-5, which can break down powerful antibiotics like meropenem, a last-resort drug in the carbapenem class. By releasing these enzyme-filled particles, the resistant bacteria were able to have a protective effect on nearby bacteria—allowing them to survive and keep growing even when treated with the antibiotic.[214]

3. Use of Antibiotics for Disease Prevention in Animals Leads to the Development of Resistance.

As stated above, the use of antibiotics inevitably leads to the development of antibiotic resistance. Administration of antibiotics in animal feed and water is no exception. The use of the

[211] Timothy M. Ghaly & Michael R. Gillings, *New Perspectives on Mobile Genetic Elements: A Paradigm Shift for Managing the Antibiotic Resistance Crisis*, 377 Phil. Transactions Royal Soc'y Biological Scis. (2021); Gang Liu, Line Elnif Thomsen & John Elmerdahl Olsen, *Antimicrobial-Induced Horizontal Transfer of Antimicrobial Resistance Genes in Bacteria: A Mini-Review*, 77 J. Antimicrobial Chemotherapy 556 (2022); Christian J.H. von Wittensdorf et al., *Dissemination of Antimicrobial Resistance in Microbial Ecosystems Through Horizontal Gene Transfer*, 7 Frontiers Microbiology (2016). *See also* 2019 NIAID Report, at 2 ("In recent decades, bacterial resistance has increased at an alarming rate. This includes resistance among gram-negative bacteria, which have acquired and spread new resistance traits especially rapidly over the past decade.").
[212] Richard J. Fair & Yitzhak Tor, *Antibiotics and Bacterial Resistance in the 21st Century*, 6 Persps. Med. Chemistry 25 (2014); Porooshat Dadgostar, *Antimicrobial Resistance: Implications and Costs*, 12 Infection & Drug Resistance 3903 (2019); Claas Kirchhelle, *The Antibiocene – Towards an Eco-Social Analysis of Humanity's Antimicrobial Footprint*, 10 Humanities & Soc. Scis. Commc'ns 1 (2023); Iruka N. Okeke et al., *The Scope of the Antimicrobial Resistance Challenge*, 403 Lancet 2426 (2024); Giedrė Valdonė Sakalauskien et al., *Unseen Enemy: Mechanisms of Multidrug Antimicrobial Resistance in Gram-Negative ESKAPE Pathogens*, 14 Antibiotics (2025).
[213] Gang Liu, Line Elnif Thomsen & John Elmerdahl Olsen, *Antimicrobial-Induced Horizontal Transfer of Antimicrobial Resistance Genes in Bacteria: A Mini-Review*, 77 J. Antimicrobial Chemotherapy 556 (2022).
[214] Lin Li et al., *NDM-5-Carried Outer Membrane Vesicles Impair the Efficacy of Antibiotics Against Bacterial Infections*, 69 Antimicrobial Agents & Chemotherapy (2025).

oral route whether by water or feed directly affects gut bacteria[215] and also increases the risk of resistance development when compared to parenteral use of antibiotic by injection.[216]

Moreover, many studies show that this general rule is true of the specific use of antibiotics for the purpose of disease prevention in animals. For example, a recent review of disease prevention in feedlot cattle stated that "[r]outine prophylaxis/metaphylaxis leads to substantial antimicrobial consumption since 'healthy' individuals will always outnumber sick individuals, in all but exceptional situations."[217]

Another study looked at preventive use of MIAs in chickens raised for meat and found the use led to "a dramatic increase in both antimicrobial resistance rates and phenotype diversity of *E. coli* strains," compared to untreated chicken.[218]

Many studies have shown the use of preventive antibiotics in pigs also leads to increased resistance. Thus, one study compared pigs raised with antibiotics at prevention doses, treatment only, or no antibiotics, and found more resistance and more multidrug resistance in fecal bacteria from pigs given MIAs at prevention doses compared to both uses for individual animal treatment and no antibiotic use.[219] Another study compared antibiotic use across 34 farms and found preventive doses of antibiotics in starter and finisher feeds "selects for and maintains antimicrobial resistance among *E. coli* for finisher pigs."[220] Yet another study comparing farms with regard to antibiotic use, found more resistance in pigs farms where MIAs were used for

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[215] Yang Zhou et al., *Antibiotic Administration Routes and Oral Exposure to Antibiotic Resistant Bacteria as Key Drivers for Gut Microbiota Disruption and Resistome in Poultry*, 11 Frontiers Microbiology (2020); Nicole Ricker et al., *Toward Antibiotic Stewardship: Route of Antibiotic Administration Impacts the Microbiota and Resistance Gene Diversity in Swine Feces*, 7 Frontiers Veterinary Sci. (2020); Tony Rochegüe et al., *Impact of Antibiotic Therapies on Resistance Genes Dynamic and Composition of the Animal Gut Microbiota*, 11 Animals 3280 (2021).
[216] *See* E. Burow et al., *Oral Antimicrobials Increase Antimicrobial Resistance in Porcine E. coli - A Systematic Review*, 113 Preventive Veterinary Med. 364 (2014); L. Schönecker et al., *Associations Between Antimicrobial Treatment Modalities and Antimicrobial Susceptibility in Pasteurellaceae and E. coli Isolated from Veal Calves Under Field Conditions*, 236 Veterinary Microbiology (2019); Csaba Varga et al., *Associations Between Reported On-Farm Antimicrobial Use Practices and Observed Antimicrobial Resistance in Generic Fecal Escherichia coli Isolated from Alberta Finishing Swine Farms*, 88 Preventive Veterinary Med. 185 (2009).
[217] Keith E. Baptiste & Niels C. Kyvsgaard, *Do Antimicrobial Mass Medications Work? A Systematic Review and Meta-Analysis of Randomised Clinical Trials Investigating Antimicrobial Prophylaxis or Metaphylaxis Against Naturally Occurring Bovine Respiratory Disease*, 75 Pathogens and Disease (2017).
[218] Paulo Martins da Costa et al., *Effects of Antimicrobial Treatment on Selection of Resistant Escherichia coli in Broiler Fecal Flora*, 14 Microbial Drug Resistance 299 (2008).
[219] *See* G. Gellin et al., *Antibiotic Resistance of Gram-Negative Enteric Bacteria from Pigs in Three Herds with Different Histories of Antibiotic Exposure*, 55 Applied & Env't Microbiology 2287 (1989). The dose for chlortetracycline was slightly less than the current preventive dose, but the dose given of virginiamycin was the same as contemporary control approvals for swine. B.E. Langlois, G. L. Cromwell & V. W. Hays, *Influence of Type of Antibiotic and Length of Antibiotic Feeding Period on Performance and Persistence of Antibiotic Resistant Enteric Bacteria in Growing-Finishing Swine*, 46 J. Animal Sci. 1383 (1978).
[220] R.H. Dunlop et al., *Associations Among Antimicrobial Drug Treatments and Antimicrobial Resistance of Fecal Escherichia Coli of Swine on 34 Farrow-to-Finish Farms in Ontario, Canada*, 34 Preventive Veterinary Med. 283 (1998).

disease prevention compared to farms where they were not.[221] Two more recent studies found the same increase in resistance on farms using antibiotics for routine disease prevention.[222]

Multiple studies have found the use of tylosin in cattle to prevent liver abscesses increases resistance to the related human drug erythromycin in bacteria from feedlot cattle.[223] A meta-analysis of preventive tylosin use in cattle found, "[w]hen fed at approved dosages for typical durations, tylosin increases the proportion of macrolide-resistant enterococci in the cattle gastrointestinal tract."[224]

b. Science is Clear That Routine Animal Antibiotic Use Significantly Harms Humans, Animals, and the Economy.

1. Antibiotics, Resistant Bacteria, and Antibiotic Resistance Genes Are Transferred from Livestock and Poultry to Humans and the Environment.

Evidence linking antibiotic use in animals to transferable resistance impacting human health has been around since the 1960s,[225] and has been frequently reaffirmed and reinforced since then. For example, the U.S. Institute of Medicine of the National Academies in a 2003 report found "[s]ubstantial evidence" that antibiotic use in food-producing animals, most of which was subtherapeutic, contributed to transmissible resistance affecting humans[226] and recommended banning the use of MIAs for growth promotion because of this evidence.[227] The 2016 Review on Antimicrobial Resistance, commissioned by the Wellcome Trust and the UK government, reviewed research on antibiotic use in food-producing animals and concluded that "antibiotic use

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[221] Disease prevention is also described as prophylactic use. M. Docic & G. Bilkei, *Differences in Antibiotic Resistance in Escherichia coli, Isolated from East-European Swine Herds with or Without Prophylactic Use of Antibiotics*, 50 J. Veterinary Med. 27 (2003).

[222] Kittitat Lugsomya et al., *Routine Prophylactic Antimicrobial Use Is Associated with Increased Phenotypic and Genotypic Resistance in Commensal Escherichia Coli Isolates Recovered from Healthy Fattening Pigs on Farms in Thailand*, 24 Microbial Drug Resistance 213 (2018); Ryohei Toya et al., *Risk of Multidrug Resistance in Escherichia coli Associated with Routine Antimicrobial Prophylaxis on Pig Farms*, 3 npj Antimicrobials & Resistance 1 (2025).

[223] Getahun E. Agga et al., *Effect of Continuous In-Feed Administration of Tylosin to Feedlot Cattle on Macrolide and Tetracycline Resistant Enterococci in a Randomized Field Trial*, 215 Preventive Veterinary Med. (2023); John W. Schmidt et al., *In-Feed Tylosin Phosphate Administration to Feedlot Cattle Minimally Affects Antimicrobial Resistance*, 83 J. Food Prot. 350 (2020); M.E. Jacob et al., *Effects of Feeding Wet Corn Distillers Grains with Solubles with or Without Monensin and Tylosin on the Prevalence and Antimicrobial Susceptibilities of Fecal Foodborne Pathogenic and Commensal Bacteria in Feedlot Cattle*, 86 J. Animal Sci. 1182 (2008); Rahat Zaheer et al., *Effect of Subtherapeutic vs. Therapeutic Administration of Macrolides on Antimicrobial Resistance in Mannheimia haemolytica and Enterococci Isolated from Beef Cattle*, 4 Frontiers Microbiology (2013); Sarah A. Murray et al., *Effects of Tylosin, a Direct-Fed Microbial and Feedlot Pen Environment on Phenotypic Resistance Among Enterococci Isolated from Beef Cattle Feces*, 11 Antibiotics (2022).

[224] Casey L. Cazer et al., *The Effect of Tylosin on Antimicrobial Resistance in Beef Cattle Enteric Bacteria: A Systematic Review and Meta-Analysis*, 176 Preventive Veterinary Med. (2020).

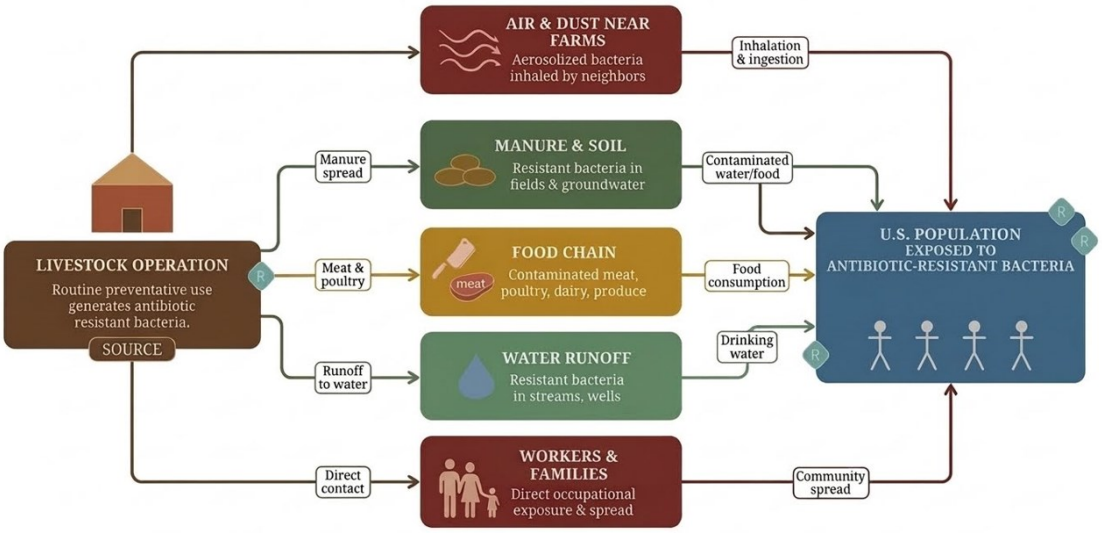
[225] W. Witte, *Selective Pressure by Antibiotic Use in Livestock*, 16 Int'l J. Antimicrobial Agents 19 (2000).

[226] Inst. of Med. (US) Comm. on Emerging Microbial Threats to Health in the 21st Century, *Microbial Threats to Health: Emergence, Detection, and Response* 208 (Mark S. Smolinski, Margaret A. Hamburg & Joshua Lederberg eds., 2003).

[227] *Id.* at 209.

in animals is a factor in promoting resistance in humans and provides enough justification for policy makers to aim to reduce global use in food production to a more optimal level."[228]

Figure 3. Pathways by Which Antibiotic-Resistant Bacteria Travel from Food-Producing Animals to Humans[229]



Food-producing animal raising facilities (often termed "concentrated animal feeding operations," or "confined animal feeding operations"—CAFOs), have long been recognized as reservoirs of antibiotic-resistant bacteria and antibiotic-resistant genes (ARGs) due to their very high usage of antibiotics.[230] But public health risks are not contained in these reservoirs. They spill out into the wider world.

Resistance to antibiotics is common in the bacterial pathogens causing the greatest amount of foodborne illness, non-typhoidal *Salmonella*[231] and *Campylobacter*.[232] These two pathogens alone count for around 20% of the resistant infections included in the 2019 CDC Threat Report.[233] In addition to these frank pathogens—pathogens that cause illness when people are exposed to them—antibiotic use in animals can contribute to resistance in colonizing

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[228] Rev. on Antimicrobial Resistance, *Antimicrobials in Agriculture and the Environment: Reducing Unnecessary Use and Waste* 1 (2015), https://amr-review.org/sites/default/files/Antimicrobials%20in%20agriculture%20and%20the%20environment%20-%20Reducing%20unnecessary%20use%20and%20waste.pdf.

[229] CDC, *Antibiotic Resistance Threats in the United States 2019*, at vii (2019), https://www.cdc.gov/antimicrobial-resistance/data-research/threats/index.html.

[230] William G. Huber et al., *Antibiotic Sensitivity Patterns and R Factors in Domestic and Wild Animals*, 22 Archives of Environmental Health 561 (1971); Frank M. Aarestrup, *The Livestock Reservoir for Antimicrobial Resistance: A Personal View on Changing Patterns of Risks, Effects of Interventions and the Way Forward*, 370 Phil. Transactions Royal Soc'y B: Biological Scis. (2015); Abigail Salyers & Nadja B. Shoemaker, *Reservoirs of Antibiotic Resistance Genes*, 17 Animal Biotechnology 137 (2006).

[231] Hyemin Oh, Yukyung Choi & Jeeyeon Lee, *Antibiotic Resistant Salmonella in Animal Products Jeopardize Human Health*, 45 Food Sci. Animal Res. 409 (2025).

[232] Ema Aleksić et al., *Resistance to Antibiotics in Thermophilic Campylobacters*, 8 Frontiers Med. (2021).

[233] CDC, *Antibiotic Resistance Threats in the United States 2019*, at 17 (2019), https://www.cdc.gov/antimicrobial-resistance/data-research/threats/index.html.

opportunistic pathogens—bacteria that can be carried by people and animals and not cause illness until the right conditions occur—such as *E. coli* and *S. aureus*.[234] Animals often harbor *E. coli* strains that colonize and make people sick, and antibiotic use in these animals leads to resistance.[235] Similarly, antibiotic use in food-producing animals has selected for resistance in *S. aureus* that causes colonization along with difficult to treat infections in people.[236] Other opportunistic pathogens such as *Klebsiella,*[237] *Enterococci,*[238] *Acinetobacter,*[239] and *Pseudomonas,*[240] can also be found in animals, on food, and transfer from animals to people after acquiring resistance in agricultural settings. The use of antibiotics in food-producing animals likely contributes to animal colonization by *Clostridioides difficile* and the subsequent contamination of food products, thereby contributing to human *C. difficile* infections.[241] All of these colonizing pathogens along with *Salmonella* and *Campylobacter* are considered urgent or serious threats by CDC.[242]

Studies of antibiotic-resistant pathogens, antibiotics, and antibiotic resistance genes show many pathways from animal agriculture to humans. Spread from animal agriculture to humans can occur via contaminated animal feed,[243] contamination of food products through water[244] and air pollution,[245] and direct exposure to animals[246] and their environment.[247] Antibiotics themselves,

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[234] Lance B. Price et al., *Colonizing Opportunistic Pathogens (COPs): The Beasts in All of Us*, 13 PLoS Pathogens (2017).
[235] Adriana Silva et al., *Antimicrobial Resistance and Clonal Lineages of Escherichia Coli from Food-Producing Animals*, 12 Antibiotics (2023).
[236] Vanessa Silva et al., *Staphylococcus aureus and MRSA in Livestock: Antimicrobial Resistance and Genetic Lineages*, 11 Microorganisms (2023).
[237] Katie Wall et al., *Klebsiella, a Hitherto Underappreciated Zoonotic Pathogen of Importance to One Health: A Short Review*, 3 Zoonoses (2023).
[238] Joana Monteiro Marques et al., *Dissemination of Enterococcal Genetic Lineages: A One Health Perspective*, 12 Antibiotics (2023).
[239] Santiago Castillo-Ramírez et al., *Acinetobacter baumannii: Much More than a Human Pathogen*, 69 Antimicrobial Agents & Chemotherapy (2025).
[240] Basma Badawy et al., *Prevalence of Multidrug-Resistant Pseudomonas aeruginosa Isolated from Dairy Cattle, Milk, Environment, and Workers' Hands*, 11 Microorganisms (2023).
[241] Declan Bolton & Pilar Marcos, *The Environment, Farm Animals and Foods as Sources of Clostridioides Difficile Infection in Humans*, 12 Foods (2023).
[242] CDC, *Antibiotic Resistance Threats in the United States 2019* (2019), https://www.cdc.gov/antimicrobial-resistance/data-research/threats/index.html.
[243] Ayidh M. Almansour et al., *The Silent Threat: Antimicrobial-Resistant Pathogens in Food-Producing Animals and Their Impact on Public Health*, 11 Microorganisms (2023).
[244] Sheridan K. Haack et al., *Genes Indicative of Zoonotic and Swine Pathogens Are Persistent in Stream Water and Sediment Following a Swine Manure Spill*, 81 Applied & Env't Microbiology 3430 (2015); Sharon P. Nappier et al., *Antibiotic Resistance in Recreational Waters: State of the Science*, Int'l J. Env't Rsch. & Pub. Health. (2020); Timothy P. Neher et al. *Catchment-Scale Export of Antibiotic Resistance Genes and Bacteria from an Agricultural Watershed in Central Iowa*, 15 PLoS ONE (2020); Renee Chowdhry et al., *Community-Engaged Course-Based Undergraduate Research of Multidrug Resistance in Escherichia coli in Water near Dairy and Hog Farms in Michigan*, 17 Env't Microbiology (2025).
[245] Ayidh M. Almansour et al., *The Silent Threat: Antimicrobial-Resistant Pathogens in Food-Producing Animals and Their Impact on Public Health*, 11 Microorganisms (2023).
[246] *See Antimicrobial Resistance, Food, and Food Animals*, CDC (May 2, 2024), https://www.cdc.gov/food-safety/foods/antimicrobial-resistance.html; Erin Frey et al., *Antimicrobial Resistance in Multistate Outbreaks of Nontyphoidal Salmonella Infections Linked to Animal Contact-United States, 2015-2018*, 62 J. Clinical Microbiology (2024).
[247] Wei Sun et al., *Exposure and Health Risks of Livestock Air Resistomes*, 122 PNAS (2025).

like other pharmaceuticals, are often detected downwind[248] and downstream of livestock facilities.[249] Moreover, livestock often excrete unchanged antibiotics in urine and feces.[250] Once released into the environment, antibiotics can continue to select for resistant bacteria, increasing the risk of human infection with resistant pathogens.[251]

Resistant bacteria and antibiotic resistance genes are also readily transferred from livestock waste into water, soil, and air where humans may inhale or ingest antibiotic-resistant bacteria.[252] For example, resistant bacteria and antibiotic resistance genes can spread from agricultural operations through discharge of wastewater from food and feedstock processing plants, and through the application of livestock manure from animal feeding operations to land.[253] A 2013 study detected methicillin-resistant *S. aureus* (MRSA) in the ambient air outside poultry barns and on the ground downwind from the barns.[254] Another 2013 study found that farm "[s]oil receiving manure was enriched in antibiotic-resistant bacteria and various antibiotic resistance determinants."[255] Consumption of produce contaminated with animal manure is a pathway through which humans are exposed to resistant bacteria.[256]A 2015

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[248] Andrew D. McEachran et al., *Antibiotics, Bacteria, and Antibiotic Resistance Genes: Aerial Transport from Cattle Feed Yards via Particulate Matter*, 123 Env't Health Persps. 337 (2015).
[249] Fabio Kaczala & Shlomo E. Blum, *The Occurrence of Veterinary Pharmaceuticals in the Environment: A Review*, 12 Current Analytical Chemistry 169 (2016); Cameron Meyer, Skyler Price & Ayse Ercumen, *Do Animal Husbandry Operations Contaminate Groundwater Sources with Antimicrobial Resistance: Systematic Review*, 31 Env't Sci. & Pollution Rsch. 16164 (2024).
[250] Ajit K. Sarmah, Michael T. Meyer & Alistair B.A. Boxall, *A Global Perspective on the Use, Sales, Exposure Pathways, Occurrence, Fate and Effects of Veterinary Antibiotics (VAs) in the Environment*, 65 Chemosphere 725 (2006); Kwon Rae Kim et al., *Occurrence and Environmental Fate of Veterinary Antibiotics in the Terrestrial Environment*, 214 Water, Air & Soil Pollution 163 (2011); Saranya Kuppusamy et al., *Veterinary Antibiotics (VAs) Contamination as a Global Agro-Ecological Issue: A Critical View*, 257 Agric. Ecosystems & Env't 47 (2018).
[251] Svetlana I. Polianciuc et al., *Antibiotics in the Environment: Causes and Consequences*, 93 Med. & Pharmacy Reps. 231 (2020).
[252] Ya He et al., *Antibiotic Resistance Genes from Livestock Waste: Occurrence, Dissemination, and Treatment*, 3 NPJ Clean Water 1 (2020).
[253] Carrie E. Givens et al., *Simultaneous Stream Assessment of Antibiotics, Bacteria, Antibiotic Resistant Bacteria, and Antibiotic Resistance Genes in an Agricultural Region of the United States*, 904 Sci. Total Env't (2023). This is particularly problematic in Iowa where antibiotic-resistant enterococci and staphylococci are ubiquitous in Iowa streams and 68% of Iowa streams exceed *E. coli* standards for primary contact. *Id*. Iowa is the leading U.S. producer of pork and eggs. *See* Iowa Dep't of Agric. & Land Stewardship, https://iowaagriculture.gov/ (last visited Apr. 7, 2026).
[254] A. Friese et al., *Occurrence of Livestock-Associated Methicillin-Resistant Staphylococcus aureus in Turkey and Broiler Barns and Contamination of Air and Soil Surfaces in Their Vicinity*, 79 Applied & Env't Microbiology 2759 (2013); *see also* Dwight D. Ferguson et al., *Detection of Airborne Methicillin-Resistant Staphylococcus aureus Inside and Downwind of a Swine Building, and in Animal Feed: Potential Occupational, Animal Health, and Environmental Implications*, 21 J. Agromedicine 149, 151 (2016) (detecting "airborne MRSA inside [a] swine facility and 215 meters downwind of the swine facility").
[255] Romain Marti et al., *Impact of Manure Fertilization on the Abundance of Antibiotic-Resistant Bacteria and Frequency of Detection of Antibiotic Resistance Genes in Soil and on Vegetables at Harvest*, 79 Applied & Env't Microbiology 5701, 5701 (2013).
[256] Food & Agric. Org. of the United Nations, WHO, *FAO/WHO Expert Meeting on Foodborne Antimicrobial Resistance: Role of Environment, Crop and Biocides* (2018), https://openknowledge.fao.org/server/api/core/bitstreams/54329186-dc44-4cac-b633-09c11464dce5/content; Tiago Lima, Sara Domingues & Gabriela Jorge da Silva, *Manure as a Potential Hotspot for Antibiotic Resistance Dissemination by Horizontal Gene Transfer Events*, 7 Veterinary Scis. (2020); Bingshen Liu et al., *Antibiotic Resistance Genes in the Animal Manure-Amended Soil-Plant System: Occurrence, Transmission, Bacterial Hosts, and Human Health Risks*, 303 Ecotoxicology & Env't Safety (2025).

study confirmed that airborne particulate matter downwind of livestock feedlots contained livestock-associated bacteria and increased levels of "genes encoding resistance to tetracycline antibiotics."[257] And a 2025 study found air in livestock facilities was highly enriched with antibiotic resistance genes compared to urban air.[258]

A recent 2025 study showed a definitive link between aerosolized cattle feedlot dust and the airborne transfer of foodborne pathogen Shiga toxin-producing *E. coli* (STEC) to adjacent and nearby agricultural fields. [259] This study sheds light[260] on the circumstances and potential dispersal pathways of STEC during one of the largest *E. coli* O157:H7 outbreaks[261] in the United States in 2018. While this study did not look at antibiotic resistance, it clearly shows bacteria containing dangerous gene—in this case genes associated with toxin production—transferring from food animals to produce.[262] Any resistance genes in the *E. coli* from the cattle were also likely transmitted.

Another critical pathway—one of great concern to the general public—is the consumption of contaminated animal-based products, such as eggs, meat, and milk.[263] Many studies highlight the critical role of retail meat products as "vehicles for the zoonotic foodborne transmission of pathogens and antimicrobial resistant bacteria" and find antibiotic-resistant bacteria on retail meat products. [264] Recent papers on individual pathogens demonstrate the links between antibiotics used in animal agriculture and human infection by resistant bacteria through the consumption of contaminated products. For example, a 2018 paper indicates that resistance in *Campylobacter,* a major bacterial foodborne pathogen, is linked to antibiotic use in animals, and that resistance complicates treatment of "severe or prolonged infections."[265] Another paper published the same year on the most common food-borne bacterial pathogen, non-typhoidal *Salmonella*, also shows that the use of antibiotics in food-producing animals is a major cause of resistance.[266] CDC recently reported a significant association between resistance in *Salmonella*

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[257] Andrew D. McEachran et al., *Antibiotics, Bacteria, and Antibiotic Resistance Genes: Aerial Transport from Cattle Feed Yards via Particulate Matter*, 123 Env't Health Persps. 337, 337 (2015).
[258] Wei Sun et al., *Exposure and Health Risks of Livestock Air Resistomes*, 122 PNAS (2025).
[259] Susan R. Leonard, *Air Microbiomes Reveal Presence of Shiga Toxin-Producing Escherichia coli in Airborne Cattle Pen Soil Adjacent to Large Feedlot*, 1000 Sci. Total Env't (2025).
[260] Natasha Gilbert, *How Factory Farm Air Pollution Can Spread Dangerous Bacteria*, Sentient (Oct. 2, 2025), https://sentientmedia.org/factory-farm-air-pollution-can-spread-dangerous-bacteria/.
[261] *FDA Investigated Multistate Outbreak of E. coli 0157:H7 Infections Linked to Romaine Lettuce from Yuma Growing Region*, FDA (Nov. 1, 2018), https://www.fda.gov/food/outbreaks-foodborne-illness/fda-investigated-multistate-outbreak-e-coli-o157h7-infections-linked-romaine-lettuce-yuma-growing.
[262] Susan R. Leonard, *Air Microbiomes Reveal Presence of Shiga Toxin-Producing Escherichia coli in Airborne Cattle Pen Soil Adjacent to Large Feedlot*, 1000 Sci. Total Env't (2025).
[263] Elliot Enshaie et al., *Livestock Antibiotics Use and Antimicrobial Resistance*, 14 Antibiotics (2025).
[264] Gregory A. Ballash, *Antimicrobial Resistant Bacteria Recovered from Retail Ground Meat Products in the US Include a Raoultella ornithinolytica Co-Harboring bla_{KPC-2} and bla_{NDM-5}*, 11 Sci. Reps. 1, 1 (2021). *See also* Dixie F. Mollenkopf et al., *Salmonella enterica and Escherichia coli Harboring blaCMY in Retail Beef and Pork Products*, 8 Foodborne Pathogens & Disease 333 (2011); Ashley M. O'Brien et al., *MRSA in Conventional and Alternative Retail Pork Products*, 7 PLoS ONE (2012); Daniel A. Tadesse et al., *Whole-Genome Sequence Analysis of CTX-M Containing Escherichia coli Isolates from Retail Meats and Cattle in the United States*, 24 Microbial Drug Resistance 939 (2018).
[265] Zhangqi Shen et al., *Antimicrobial Resistance in Campylobacter spp*, 6 Microbiology Spectrum 1, 1 (2018).
[266] Patrick F. McDermott, Shaohua Zhao & Heather Tate, *Antimicrobial Resistance in Nontyphoidal Salmonella*, 6 Microbiology Spectrum 6 (2018).

and hospitalization among people in the U.S. suffering from *Salmonella*.[267]

Several recent studies have confirmed earlier findings that antibiotic-resistant bacteria are also transmitted to people through direct exposure to farms or livestock. For example, it is well understood that farmworkers who often lack access to adequate healthcare or PPE, and who often labor in unsafe workplaces, are particularly susceptible to infection by antibiotic resistant bacteria.[268] One study of farmworkers in North Carolina found that workers at conventional (that is, antibiotic-using) farm facilities were more likely to carry livestock-associated MRSA and multidrug-resistant *S. aureus* than workers at antibiotic-free facilities.[269]A 2020 meta-analysis found that workers, particularly swine workers, are at significantly higher risk for livestock-associated MRSA colonization and subsequent infection compared to "control" populations—individuals who have close proximity to colonized animals but no or minimal direct contact with them, including household and community members of farmers.[270] A 2015 study of Iowans similarly found that "[c]urrent swine workers are 6 times more likely to carry [multidrug-resistant *S. aureus*] than those without current swine exposure,"[271] while a 2014 study of hospital patients in Iowa found that patients who lived within one mile of "large swine facilities" were nearly twice as likely to carry MRSA.[272] A study in Pennsylvania found a significant association between proximity to farms and crop fields fertilized with swine manure and the prevalence of skin or soft-tissue MRSA infections.[273] And workers on swine farms have been shown to have higher resistance gene loads than workers in poultry raising facilities (which have much lower antibiotic use) or controls not working on farm.[274]

In summary, studies have identified increasing numbers of environmental sources of resistance,[275] many linked to food-animal production. This includes the food supply,[276] in the

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[267] Louise K. Francois Watkins et al., *Clinical Outcomes of Patients with Nontyphoidal Salmonella Infections by Isolate Resistance—Foodborne Diseases Active Surveillance Network, 10 US Sites, 2004–2018*, 78 Clinical Infectious Diseases 535 (2024).
[268] *See* Roxanne Khamsi, *Why Farm Workers Need Protection from Antimicrobial Resistance*, Nature (May 13, 2026), https://www.nature.com/articles/d41586-026-01377-z.
[269] Jessica L. Rinsky et al., *Livestock-Associated Methicillin and Multidrug Resistant Staphylococcus aureus Is Present Among Industrial, Not Antibiotic-Free Livestock Operation Workers in North Carolina*, 8 PLOS ONE 1 (2013).
[270] Chen Chen & Felicia Wu, *Livestock-Associated Methicillin-Resistant Staphylococcus aureus (LA-MRSA) Colonisation and Infection Among Livestock Workers and Veterinarians: A Systematic Review and Meta-Analysis*, 78 Occupational & Env't Med. 530 (2020).
[271] Shylo E. Wardyn et al., *Swine Farming Is a Risk Factor for Infection with and High Prevalence of Carriage of Multidrug-Resistant Staphylococcus aureus*, 61 Clinical Infectious Diseases 59, 59 (2015).
[272] Margaret Carrel et al., *Residential Proximity to Large Numbers of Swine in Feeding Operations Associated with Increased Risk of Methicillin-Resistant Staphylococcus aureus Colonization at Time of Hospital Admission in Rural Iowa Veterans*, 35 Infection Control & Hospital Epidemiology 190, 190 (2014).
[273] Joan A. Casey et al., *High-Density Livestock Operations, Crop Field Application of Manure, and Risk of Community-Associated Methicillin-Resistant Staphylococcus aureus Infection in Pennsylvania*, 173 JAMA Internal Med. 1980 (2013).
[274] Liese van Gompel et al., *Description and Determinants of the Faecal Resistome and Microbiome of Farmers and Slaughterhouse Workers: A Metagenome-Wide Cross-Sectional Study*, 143 Env't Int'l (2020).
[275] Nicholas Skandalis et al., *Environmental Spread of Antibiotic Resistance*, 10 Antibiotics (2021).
[276] Patricia Antunes, Carla Novais & Luísa Peixe, *Food-to-Humans Bacterial Transmission*, 8 Microbiology Spectrum (2020); María G. Balbuena-Alonso et al., *Genomic Analysis of Plasmid Content in Food Isolates of E. coli Strongly Supports Its Role as a Reservoir for the Horizontal Transfer of Virulence and Antibiotic Resistance Genes*, Plasmid 123 (2022); Katarzyna Grudlewska-Buda et al., *Antibiotic Resistance in Selected Emerging Bacterial*

air,[277] soils,[278] rivers and streams near and down from animal operations. Decades of widespread antibiotic use in humans and animals have created environmental reservoirs of resistance genes, which, together with ongoing selection pressure, foster the emergence of new resistant pathogens[279] and exacerbate the threat of difficult or impossible to treat bacterial infections.[280]

2. Genetic Studies Confirm that Resistant Bacteria Are Transmitted Between Food Producing Animals and People.

Genetic studies also provide strong evidence that resistant bacteria and mobile genetic material conferring resistance are transmitted between livestock and humans, through direct contact and through the food supply. A 2025 study found a high degree of genetic similarity between *Salmonella* Dublin isolates from cattle and those causing illness in people.[281] The clinical isolates from cattle exhibited greater antibiotic resistance, suggesting likely transfer of this *Salmonella* strain from cattle to people. Another recent study found that cattle can be "a source of *C. jejuni* infecting people through a transmission pathway from cattle to people via the consumption of chicken."[282] Over half of human *Campylobacter* infections between 2005 and 2021 have been

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Foodborne Pathogens—An Issue of Concern?, 12 Antibiotics (2023); Martin A. Makary, Katerina Kaczmarski & Keeve Nachman, *A Call for Doctors to Recommend Antibiotic-Free Foods: Agricultural Antibiotics and the Public Health Crisis of Antimicrobial Resistance*, 71 J. Antibiotics 685 (2018); Aron R. Mebrahtu et al., *A Systematic Review and Meta-Analysis of Antibiotic Resistance of Foodborne Pathogenic Bacteria*, 25 BMC Infectious Diseases (2025).

[277] Paul B.L. George et al., *Antimicrobial Resistance in the Environment: Towards Elucidating the Roles of Bioaerosols in Transmission and Detection of Antibacterial Resistance Genes*, 11 Antibiotics (2022); Anna Kozajda, Emilia Miśkiewicz & Karolina Jeżak, *Zoonotic Bacteria in the Vicinity of Animal Farms as a Factor Disturbing the Human Microbiome: A Review*, 37 Health 138 (2024); Lucia Maestre-Carballa, Vicente Navarro-López & Manuel Martinez-Garcia, *Metagenomic Airborne Resistome from Urban Hot Spots Through the One Health Lens*, 16 Env't Microbiology Reps. (2024).

[278] Ya He et al., *Antibiotic Resistance Genes from Livestock Waste: Occurrence, Dissemination, and Treatment*, 3 npj Clean Water (2020); Brim S. Ondon et al., *Sources of Antibiotic Resistant Bacteria (ARB) and Antibiotic Resistance Genes (ARGs) in the Soil: A Review of the Spreading Mechanism and Human Health Risks*, 256 Revs. Env't Contamination & Toxicology 121 (2021); Abdullah K. Rad et al., *An Overview of Antibiotic Resistance and Abiotic Stresses Affecting Antimicrobial Resistance in Agricultural Soils*, 19 Int'l J. Env't Rsch. & Pub. Health (2022).

[279] Daniel Martak, Charles P. Henriot & Didier Hocquet, *Environment, Animals, and Food as Reservoirs of Antibiotic-Resistant Bacteria for Humans: One Health or More?*, 54 Infectious Diseases Now (2024).

[280] Porooshat Dadgostar, *Antimicrobial Resistance: Implications and Costs*, 12 Infection & Drug Resistance 3903 (2019).

[281] Sophia M. Kenney, Nkuchia M. M'ikanatha & Erika Ganda, *Genomic Evolution of Salmonella Dublin in Cattle and Humans in the United States*, 91 Applied & Env't Microbiology (2025).

[282] Januana S. Teixeira et al., *Molecular Epidemiological Evidence Implicates Cattle as a Primary Reservoir of Campylobacter jejuni Infecting People via Contaminated Chickens*, 11 Pathogens 1, 1 (2022). Generally speaking, it is important for FDA to consider epidemiological studies as they have been foundational to understanding public health harms and risks. For example, links between certain occupations and incidences of cancer were discovered through the precursors to epidemiological studies. *See* Dana Loomis et al., *Identifying Occupational Carcinogens: An Update from the IARC Monographs*, 75 Occupational & Env't Med. 593 (2018). Epidemiological studies have also helped establish links between airborne lead exposure and elevated blood lead levels in children, and between perfluorooctanoic acid and perfluorooctane sulfonate and a host of diseases. *See* Marie Lynn Miranda, Rebecca Anthopolos & Douglas Hastings, *A Geospatial Analysis of the Effects of Aviation Gasoline on Childhood Blood Lead Levels*, 119 Env't Health Persps. 1513 (2011); Stephanie J. Frisbee et al., *The C8 Health Project: Design, Methods, and Participants*, 117 Env't Health Persps. 1873 (2009); *The Science Panel*, C8 Science Panel, http://www.c8sciencepanel.org/index.html (last updated Jan. 22, 2020). Epidemiological studies have been used by the federal government when engaging in regulatory action. For example, EPA has used epidemiological studies to

resistant to at least one antibiotic.[283]

A 2012 study of *E. coli* bacteria isolated from pigs found resistance genes on plasmids that are highly similar to plasmids frequently observed in human *E. coli* samples.[284] This observation provides evidence that plasmids are transferred between livestock and humans. Similarly, a genetic study of antibiotic-resistant *E. coli* isolates from humans and chicken meat found that 40% of the *E. coli* from human samples were closely related to those isolated from chicken meat. The authors concluded that "chicken meat is a likely contributor to the recent emergence of [resistant *E. coli*] in human infections in the study region."[285]

In 2024, researchers at George Washington University used a novel statistical approach and whole genome sequencing to estimate the proportion of pediatric urinary tract infections (UTIs) caused by foodborne *E. coli* strains. [286] They estimated that 19% of the clinical *E. coli* isolates were foodborne zoonotic strains, suggesting that, "a substantial portion of pediatric UTIs in the Washington DC region may be caused by *E. coli* strains originating in food animals and likely transmitted via contaminated poultry meat." [287] A related 2025 study found that 18% of *E. coli* UTIs including resistant infections likely originated in food-producing animals.[288]

Another genetic study found evidence that a particular strain of MRSA found in livestock originated as methicillin-susceptible *S. aureus* in humans. The strain "jump[ed] from humans to livestock, where it subsequently acquired tetracycline and methicillin resistance."[289] These findings are consistent with a 2015 study's observation that several antibiotic-resistant genes

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set air quality standards, and such studies were also foundational for the agency's setting of lead levels for air and water, as well as for certain products such as paint. Douglas W. Dockery et al., *An Association Between Air Pollution and Mortality in Six U.S. Cities*, 329 New England J. Med. 1753 (1993); Herbert L. Needleman et al., *Deficits in Psychologic and Classroom Performance of Children with Elevated Dentine Lead Levels*, 300 New England J. Medicine 689 (1979); EPA, *Air Quality Criteria for Lead, Vol III*, at 12-86 to 12-88, 12-95 (1986), https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=32647; Maximum Contaminant Level Goals and National Primary Drinking Water Regulations for Lead and Copper, 56 Fed. Reg. 26460, 26468–69 (June 7, 1991); Lead; Identification of Dangerous Levels of Lead, 63 Fed. Reg. 30302, 30316–17 (June 3, 1998). The final rule was published at 66 Fed. Reg. 1206 (Jan. 5, 2001). National Ambient Air Quality Standards for Lead, 73 Fed. Reg. 66964 (Nov. 12, 2008).

[283] *NARMS Now: Integrated Data*, FDA, https://www.fda.gov/animal-veterinary/national-antimicrobial-resistance-monitoring-system/narms-now-integrated-data (last updated Mar. 23, 2026) (select "Multidrug Resistance by Number of Antimicrobial Classes," then select "Campylobacter" for "Bacterium," "(All)" for "Species or serotype," ">=1 Antimicrobial Classes)" for "Number of antimicrobial classes," and "Humans" for "Source(s).").

[284] Yvonne Agersø et al., *Prevalence of Extended-Spectrum Cephalosporinase (ESC)-Producing Escherichia coli in Danish Slaughter Pigs and Retail Meat Identified by Selective Enrichment and Association with Cephalosporin Usage*, 67 J. Antimicrobial Chemotherapy 582 (2012).

[285] Jan A. J. W. Kluytmans et al., *Extended-Spectrum β-Lactamase-Producing Escherichia coli from Retail Chicken Meat and Humans: Comparison of Strains, Plasmids, Resistance Genes, and Virulence Factors*, 56 Clinical Infectious Diseases 478 (2013).

[286] Maliha Aziz et al., *Pediatric Urinary Tract Infections Caused by Poultry-Associated Escherichia coli*, 12 Microbiology Spectrum 1 (2024).

[287] *Id.* at 1.

[288] Maliha Aziz et al., *Zoonotic Escherichia coli and Urinary Tract Infections in Southern California*, 16 Clinical Microbiology (2025).

[289] Lance B. Price et al., *Staphylococcus aureus CC398: Host Adaptation and Emergence of Methicillin Resistance in Livestock*, 3 mBio 1, 1 (2012).

found in human *S. aureus* may have originated in animals.[290]

3. *The Use of Antibiotics in Livestock and Poultry and the Prevalence of Resistant Bacteria in Animals, Humans, and Animal Products Are Correlated.*

Studies have produced evidence that livestock that are fed antibiotics are more likely to carry bacteria that are resistant to those antibiotics. A 2012 study of pigs in Denmark found that 11% of pigs carry *E. coli* resistant to cephalosporins. The authors observed "a significantly higher prevalence [of resistance] . . . among pigs originating from farms with registered cephalosporin consumption."[291] Even more troublingly, studies also continue to find a correlation between the use of antibiotics in livestock and an increase in the prevalence of resistance to those antibiotics in bacteria isolated from humans. For example, a modeling study found that "animal antibiotic consumption was positively linked with resistance in critical priority human pathogens."[292]

Indeed, a growing body of evidence shows that regions with higher antibiotic use in humans and animals also experience higher levels of resistance. Multiple European studies—where data on antibiotic use and resistance are available for both humans and animals—have consistently demonstrated that countries with higher levels of antibiotic use in animals show higher levels of resistance in animals, and that elevated resistance in animals contributes to increased resistance in human pathogens.[293]A 2013 study of intestinal bacteria samples from people in several European countries and the U.S. found a significantly higher prevalence of genes conferring resistance to antibiotics that were approved for animal use than genes conferring resistance to other antibiotics.[294] Another study of 176 conventional pig farms from nine European countries. found that, "[m]ajor components of the pig resistome are positively and independently associated with on-farm AMU and biosecurity conditions."[295] Researchers discovered that total AMU during the fattening phase of swine farming was positively associated with total

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[290] A. Friese et al., *Occurrence of Livestock-Associated Methicillin-Resistant Staphylococcus aureus in Turkey and Broiler Barns and Contamination of Air and Soil Surfaces in Their Vicinity*, 79 Applied & Env't Microbiology 2759 (2013).

[291] Yvonne Agersø et al., *Prevalence of Extended-Spectrum Cephalosporinase (ESC)-Producing Escherichia coli in Danish Slaughter Pigs and Retail Meat Identified by Selective Enrichment and Association with Cephalosporin Usage*, 67 J. Antimicrobial Chemotherapy 582, 582 (2012).

[292] Kasim Allel et al., *Global Antimicrobial-Resistance Drivers: An Ecological Country-Level Study at the Human–Animal Interface*, 7 Lancet Planetary Health e291, e291 (2023).

[293] Ilias Chantziaras et al., *Correlation Between Veterinary Antimicrobial Use and Antimicrobial Resistance in Food-Producing Animals: A Report on Seven Countries*, 69 J. Antimicrobial Chemotherapy 827 (2014); Eur. Ctr. Disease Prevention & Control, Eur. Food Safety Auth. & Eur. Meds. Agency, *Third Joint Inter-Agency Report on Integrated Analysis of Consumption of Antimicrobial Agents and Occurrence of Antimicrobial Resistance in Bacteria from Humans and Food-Producing Animals in the EU/EEA: JIACRA III 2016-2018*, 19 EFSA J. (2021).

[294] Kristoffer Forslund et al., *Country-Specific Antibiotic Use Practices Impact the Human Gut Resistome*, 23 Genome Rsch. 1163 (2013). As discussed above, several older studies from Spain and the United States have also found a correlation between livestock antibiotic use and an increase in the prevalence of antibiotic resistance in bacteria isolated from humans. *See* Amita Gupta et al., *Antimicrobial Resistance Among Campylobacter Strains, United States, 1997-2001*, 10 Emerging Infectious Diseases 1102, 1106–07 (2004); Stuart B. Levy et al., *Changes in Intestinal Flora of Farm Personnel After Introduction of a Tetracycline-Supplemented Feed on a Farm*, 295 New England J. Med. 583, 587 (1976).

[295] Liese van Gompel et al., *The Antimicrobial Resistome in Relation to Antimicrobial Use and Biosecurity in Pig Farming, A Metagenome-Wide Association Study in Nine European Countries*, 74 J. Antimicrobial Chemotherapy 865, 865 (2019).

antibiotic resistance genes.[296] "Positive associations were particularly observed between widely used macrolides and tetracyclines, and antibiotic resistance genes corresponding to the respective antimicrobial classes."[297] Relatedly, a recent paper looking at antibiotic use and resistance data from Europe found a significant impact from use in animals on resistance in both animals and humans as well as an impact from use in humans on resistance in animals.[298] And another study looking at data from the 30 largest animal-producing countries found that increased antibiotic use in food animals is associated with increased resistance in humans.[299]

4. Antibiotic Resistance in Humans Causes Significant Health Harms.

At least 2.8 million drug-resistant infections occur in the U.S. each year and result in over 35,000 deaths.[300] A recent Lancet study estimated that in 2021, antibiotic-resistant bacteria directly caused more than 1 million deaths worldwide and contributed to over 4.7 million deaths overall.[301] Deaths due to worsening resistance are forecast to increase by almost 70% from 2022 to 2050; in the next quarter century, more than 39 million people could die from antibiotic-resistant infections.[302]

For several decades after the discovery of penicillin, novel classes of man-made antibiotics were being developed and sold. Collectively, this antibiotic toolbox was very effective for treating bacterial infections in sick people, as well as animals. The most useful antibiotics—those that were least toxic, least likely to incur an allergic response, or those effective against a broader range of bacteria—were often the most used, as well. As resistance to these previously effective drugs has increased, the antibiotic alternatives often are less effective, more expensive, and carry more risks to patients.[303]

As resistance increases, infections on the whole have become more persistent because there are fewer antibiotics for treating them effectively and safely. From a patient's perspective, increasingly resistant bacteria translate into more treatment failures, meaning worse infections and a higher likelihood of death. These also result in longer and more frequent hospital stays, excess surgeries, and other negative impacts on patients.[304] For example, many studies have described the negative outcomes attendant to infections caused by drug-resistant strains of non-

[296] *Id*.
[297] *Id*.
[298] Sakib Rahman & Aidan Hollis, *The Effect of Antibiotic Usage on Resistance in Humans and Food-Producing Animals: A Longitudinal, One Health Analysis Using European Data*, 11 Frontiers Pub. Health (2023).
[299] Zahra Ardakani et al., *Evaluating the Contribution of Antimicrobial Use in Farmed Animals to Global Antimicrobial Resistance in Humans*, 17 One Health (2023).
[300] CDC, *Antibiotic Resistance Threats in the United States 2019*, at vii (2019), https://www.cdc.gov/antimicrobial-resistance/data-research/threats/index.html.
[301] GBD 2021 Antimicrobial Resistance Collaborators, *Global Burden of Bacterial Antimicrobial Resistance 1990–2021: A Systematic Analysis with Forecasts to 2050*, 404 Lancet 1199, 1199 (2024).
[302] *Id.* at 1199, 1213.
[303] G. L. French, *Clinical Impact and Relevance of Antibiotic Resistance*, 57 Advanced Drug Delivery Revs. 1514 (2005).
[304] N.D. Friedman, E. Temkin & Y. Carmeli, *The Negative Impact of Antibiotic Resistance*, 22 Clinical Microbiology & Infection 416 (2016).

typhoidal *Salmonella*[305] and *Campylobacter*.[306] Notably, these are the two most common bacterial causes of human infections transmitted from food-producing animals via a contaminated food supply.[307]

While anyone can suffer from an antibiotic-resistant infection, the very young and the elderly are particularly susceptible to resistant infections. Older patients are more susceptible to resistant infections that increase illness, death and healthcare costs,[308] while in neonates, 30% of sepsis deaths are a result of resistant infections.[309]

Bacterial infections are a predictable and frequent complication of many modern medical procedures, including organ transplants, joint replacements, and other major surgeries, cancer chemotherapy, and kidney dialysis. The patients needing these procedures rely on antibiotics to protect them from those complications. As antibiotic resistance grows, physicians may judge that the heightened risk of untreatable infections outweighs the expected advantages of carrying out the procedure.[310] Infection is the second leading cause of death in patients with cancer, and antibiotic resistance contributes significantly to these deaths.[311]

Treating very sick patients with antibiotics can be lifesaving. To be lifesaving, however, antibiotics must be effective against disease-causing bacteria. But the more we use antibiotics, the less effective they become. Decades ago, renowned infectious disease physician, Stuart Levy, wrote about this dilemma in his landmark book, "The Antibiotic Paradox."[312]

The U.S. is among the world's largest consumers of antibiotics, driven in part by its sizeable human population and an even larger livestock population exceeding nine billion animals.[313] Levy's paradox is why CDC emphasizes the health and safety imperative to reduce antibiotic use

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[305] Louise K. Francois Watkins et al., *Clinical Outcomes of Patients with Nontyphoidal Salmonella Infections by Isolate Resistance – Foodborne Diseases Active Surveillance Network, 10 US Sites, 2004–2018*, 78 Clinical Infectious Diseases 535 (2024); Chaelin Kim et al., *Length of Hospital Stay and Associated Treatment Costs for Patients with Susceptible and Antibiotic-Resistant Salmonella Infections: A Systematic Review and Meta-Analysis*, 15 BMJ Open (2025); Jay K. Varma et al., *Hospitalization and Antimicrobial Resistance in Salmonella Outbreaks, 1984–2002*, 11 Emerging Infectious Diseases 943 (2005).

[306] Guillermo M. Ruiz-Palacios, *The Health Burden of Campylobacter Infection and the Impact of Antimicrobial Resistance: Playing Chicken*, 44 Clinical Infectious Diseases 701 (2007); Yichao Yang et al., *A Historical Review on Antibiotic Resistance of Foodborne Campylobacter*, 10 Frontiers Microbiology (2019).

[307] Norma Heredia & Santos García, *Animals as Sources of Food-Borne Pathogens: A Review*, 4 Animal Nutrition 250 (2018).

[308] Nikolaos Theodorakis et al., *Antibiotic Resistance in the Elderly: Mechanisms, Risk Factors, and Solutions*, 12 Microorganisms (2024).

[309] Laura Folgori et al., *Tackling Antimicrobial Resistance in Neonatal Sepsis*, 5 Lancet Glob. Health e1066, e1067 (2017).

[310] Iruka N. Okeke et al., *The Scope of the Antimicrobial Resistance Challenge*, 403 Lancet 2426 (2024).

[311] Amila K. Nanayakkara et al., *Antibiotic Resistance in the Patient with Cancer: Escalating Challenges and Paths Forward*, 71 CA Cancer J. Clinicians 488 (2021).

[312] Stuart Levy, *The Antibiotic Paradox: How the Misuse of Antibiotics Destroy Their Curative Powers* 296 (2d ed. 2002); Richard P. Wenzel, *The Antibiotic Paradox: How the Misuse of Antibiotics Destroys Their Curative Powers*, 347 New England J. Med 1213 (2002) (book review).

[313] USDA, *Chapter 1: United States Data*, *in 2022 Census of Agriculture* (2024), https://www.nass.usda.gov/Publications/AgCensus/2022/Full_Report/Volume_1,_Chapter_1_US/usv1.pdf.

generally, and more specifically to reduce use that is inappropriate and therefore unnecessary—also known as improved antibiotic stewardship.[314]

Like all medications, antibiotics can cause collateral damage, in addition to selecting for antibiotic resistance. Avoiding unnecessary antibiotic use safeguards both individual safety and public health.[315]

5. Antibiotic Resistance Harms Animals and the Economy.

In addition to harming human health, the economic burden of antibiotic resistance on healthcare is immense, driven by more frequent and severe illnesses and the increased use of costly medications. In the U.S., antibiotic resistance could increase the cost to the hospital bill for treating patients with any bacterial infections by approximately $1400.[316] Globally, antibiotic resistance increases the annual cost of health care by an estimated $66 billion, and this will rise to $159 billion by 2050 without more action to combat the spread of resistance.[317]

Antibiotic resistance also impacts the health and welfare of food-producing animals[318] and has the potential to impact the production of food with an estimated cumulative global cost related to lost productivity estimated to be over $575 billion by 2050.[319]

c. Routine Antibiotic Use Is Not Necessary for Raising Livestock and Poultry.

The evidence from the chicken industry and parts of the cattle industry show that it is possible under U.S. conditions to raise livestock and poultry with low levels of antibiotics. Evidence from multiple European countries indicate that it is possible to raise pigs and cattle with much lower levels of antibiotic use than takes place on U.S. farms and feedlots, on average.[320]

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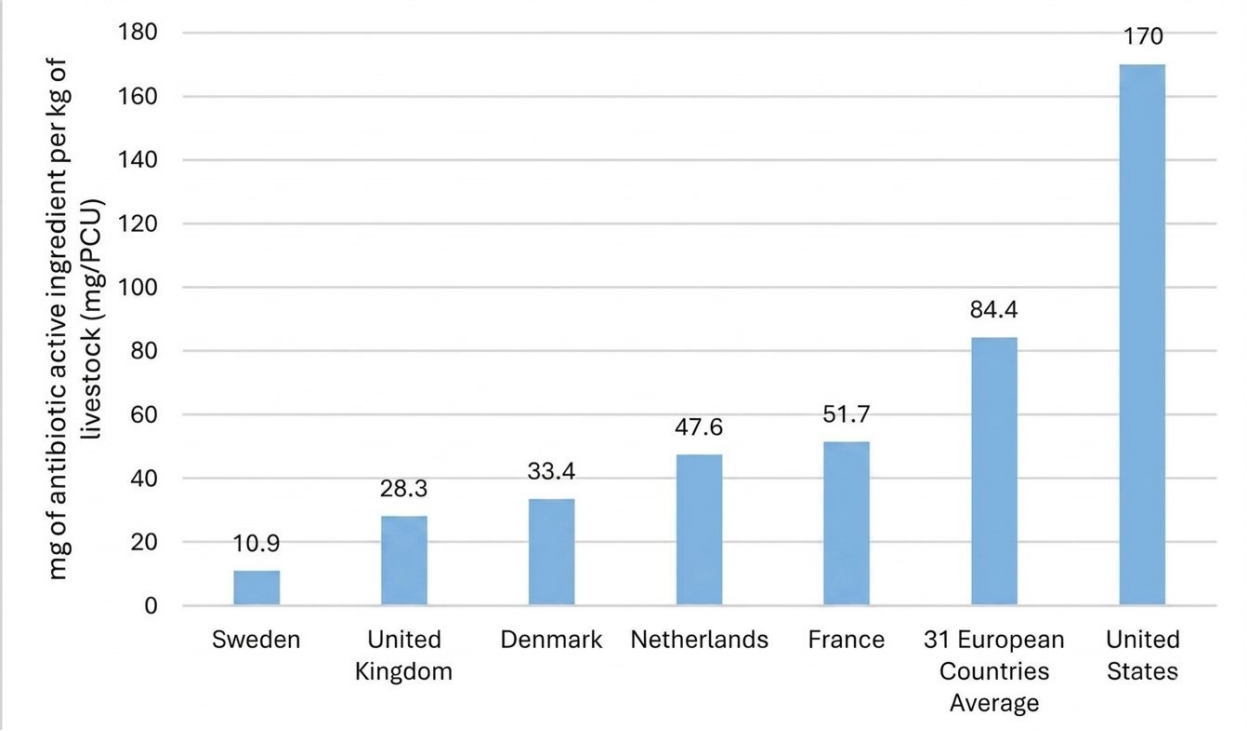
[314] *Antibiotic Use and Stewardship in the United States, 2025 Update: Progress and Opportunities*, CDC (Feb. 9, 2026), https://www.cdc.gov/antibiotic-use/hcp/data-research/stewardship-report.html.
[315] *Id.*
[316] Porooshat Dadgostar, *Antimicrobial Resistance: Implications and Costs*, 12 Infection & Drug Resistance 3903, 3906 (2019).
[317] A. McDonnell et al., *Forecasting the Fallout from AMR: Economic Impacts of Antimicrobial Resistance in Humans – A Report from the EcoAMR Series*, at x (2024), https://www.woah.org/app/uploads/2024/09/forecasting-fallout-amr-economic-impacts-antimicrobial-resistance-humans-27924-compressed.pdf.
[318] Björn Bengtsson & Christina Greko, *Antibiotic Resistance—Consequences for Animal Health, Welfare, and Food Production*, 119 Upsala J. Med. Scis. 96 (2014).
[319] B.A. Adamie et al., *Forecasting the Fallout from AMR: Economic Impacts of Antimicrobial Resistance in Food-Producing Animals – A Report from the EcoAMR Series*, at x (2024), https://www.woah.org/app/uploads/2024/09/ecoamr-woah-animal-sector-web-reduced-23924.pdf.
[320] David Wallinga & Avinash Kar, *Very High Livestock Antibiotic Use Undercuts Effective Drugs: Beef and Pork Industries Must Do Better to Help Curb Antibiotic Resistance*, Nat. Res. Def. Council (Dec. 12, 2019), https://www.nrdc.org/bio/david-wallinga-md/very-high-livestock-antibiotic-use-undercuts-effective-drugs.

Figure 10. Intensity of Antibiotic Use in Food-Producing Animals: United States Compared to Peer Nations (2021)[321]



[321] All figures are expressed in milligrams of antibiotic active ingredient per kilogram of livestock biomass (mg/PCU — population correction unit), the standard metric used by the European Medicines Agency (EMA) since 2010. This metric adjusts for differences in the size and composition of national livestock populations, enabling valid cross-country comparison. *See* Eur. Meds. Agency, *Sales of Veterinary Antimicrobial Agents in 31 European Countries in 2021: Trends from 2010 to 2021* (2022), https://www.ema.europa.eu/en/documents/report/sales-veterinary-antimicrobial-agents-31-european-countries-2021-trends-2010-2021-twelfth-esvac-report_en.pdf; David Wallinga, *FDA's Antibiotic Stewardship Plan Is Failing*, NRDC (Dec. 13, 2022), https://www.nrdc.org/bio/david-wallinga-md/fdas-antibiotic-stewardship-plan-failing (calculating U.S. figure of 170 mg/PCU based on 2021 USDA data on inventories, slaughter, and import and export of food producing animals, FDA's 2021 Summary Report, and data from the European Surveillance of Veterinary Antimicrobial Consumption's interactive database); FDA, *2021 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals* (2022), https://www.fda.gov/media/163739/download?attachment. The Netherlands figure of 44 mg/PCU represents a 73% reduction from 165 mg/PCU in 2009, demonstrating that rapid, dramatic reductions are achievable without abandoning intensive livestock production. Sweden has maintained among the lowest antibiotic use rates in Europe since banning preventive mass medication in 1986. David Walling, *European Action Halves Livestock Antibiotic Use*, NRDC (Dec. 1, 2022), https://www.nrdc.org/bio/david-wallinga-md/european-action-halves-livestock-antibiotic-use; Eur. Meds. Agency, *European Sales and Use of Antimicrobials for Veterinary Medicine: Annual Surveillance Report for 2023*, at 8 (2025), https://www.ema.europa.eu/en/documents/report/european-sales-use-antimicrobials-veterinary-medicine-annual-surveillance-report-2023_en.pdf (setting EU 2030 target of 59.2 mg/PCU).

The available data indicates that there are large variations between sectors and between farms and feedlots within sectors with respect to use of MIAs and antibiotics more broadly. In the U.S., as described above, the chicken industry uses ten times less MIAs per pound of meat produced than the cattle and swine industries. In feedlot cattle, most antibiotics are administered through feed, but a recent USDA study found that over half of all feedlots gave no antibiotics in feed, including over 30% of the largest feedlots.[322] For pigs, the data are more complicated because a significant proportion of antibiotics are administered in water as well as feed. The 2021 USDA swine data does not specify which sites avoided antibiotic use in both feed and water. However, more than 20% of sites raising nursery pigs in traditional systems reported no antibiotic use in feed, and over 30% reported no use in water—indicating that many pig farms are operating without antibiotics in these ways.[323]

d. Studies Show that Sufficiently Reducing Antibiotic Uses in Livestock and Poultry Has Reduced the Prevalence of Resistance.

Antibiotic resistance driven by unsafe excessive use of antibiotics is a solvable problem. Studies demonstrate without doubt that reduction of exposure to antibiotics reduces the prevalence of antibiotic resistance and thus is an effective policy to achieve the FFDCA's overarching goal of ensuring that the public is protected from drugs not shown to be safe.

For example, two large systemic reviews published in 2017 and 2018 found clear evidence that reducing use of antibiotics in food-producing animals reduced resistance in the animals and also was associated with lowered resistance levels in humans.[324] The authors of one of these systemic reviews later showed restrictions on antibiotic use were associated with reductions in antibiotic resistance genes in bacteria.[325]

A 2010 study in Canada found that the prevalence of ceftiofur resistance in retail poultry samples declined sharply following hatcheries' voluntary decision in 2005 to temporarily stop administering ceftiofur to chicken embryos. [326] After 2007, when ceftiofur was reintroduced, ceftiofur resistance significantly increased among *E. coli* isolates from retail chicken samples.[327]

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[322] USDA, *Management Practices on U.S. Feedlots, 2021*, at 54 tbl. G.5.a (2024), https://www.aphis.usda.gov/sites/default/files/feedlot-health-2021-mgmt-practice-dr1.pdf.
[323] USDA, *Swine Part II: NAHMS 2021 – Reference of Management Practices on Large-Enterprise Swine Operations in the United States* tbl. C.5.f. (2021), https://www.aphis.usda.gov/livestock-poultry-disease/nahms/swine/swine-2021-part-ii-reference-management-practices-large; *id.* at tbl. C.5.c.
[324] Anna Mae Scott et al., *Is Antimicrobial Administration to Food Animals a Direct Threat to Human Health? A Rapid Systematic Review*, 52 Int'l J. Antimicrobial Agents 316 (2018); Karen L. Tang et al., *Restricting the Use of Antibiotics in Food-Producing Animals and Its Associations with Antibiotic Resistance in Food-Producing Animals and Human Beings: A Systematic Review and Meta-Analysis*, 1 Lancet Planetary Health e316 (2017); *see also* Sophia M. Kenney, Nkuchia M. M'ikanatha & Erika Ganda, *Genomic Evolution of Salmonella Dublin in Cattle and Humans in the United States*, 91 Applied & Env't Microbiology (2025).
[325] Diego B. Nobrega et al., *Prevalence of Antimicrobial Resistance Genes and Its Association with Restricted Antimicrobial Use in Food-Producing Animals: A Systematic Review and Meta-Analysis*, 76 J. Antimicrobial Chemotherapy 561 (2021).
[326] Lucie Dutil et al., *Ceftiofur Resistance in Salmonella enterica Serovar Heidelberg from Chicken Meat and Humans, Canada*, 16 Emerging Infectious Diseases 48 (2010).
[327] *Id.*

Similarly, a 2013 study in Denmark found that a voluntary ban on the use of cephalosporin in pigs instituted in 2010 was followed by a significant decline in cephalosporin resistance in *E. coli* isolated from pigs. [328] In 2009, 10.8% of samples were resistant, and in 2011, only 3.9% were resistant.[329] Denmark also severely restricts the use of fluoroquinolones.[330] Data collected by the Danish Integrated Antimicrobial Resistance Monitoring and Research Programme have shown that imported broiler meat is much more likely to carry fluoroquinolone-resistant bacteria than domestic Danish meat, and *Campylobacter jejuni* infections acquired by humans traveling outside Denmark are much more likely to be resistant to fluoroquinolones than *Campylobacter* contracted in Denmark.[331]

Similarly, in the Netherlands "[a] combination of compulsory and voluntary actions with clear reduction goals" for antibiotic use have resulted in a "systematic and substantial decrease in resistance levels for a number of antimicrobials" in isolates from broilers, veal calves, and pigs.[332] Researchers there collected retail chicken meat between December 2013 and August 2015, testing 346 meat samples for the presence of ESBL-E bacteria (including mostly *E. coli*, but also *Klebsiella pneumoniae* and *Escherichia fergusonii*). [333] Over one year, researchers found a significant drop in ESBL-E contamination of retail chicken meat from a prevalence of 68.3% in 2014 to 44.6% in 2015 following significant reductions in antibiotic sales between 2009 and 2014. [334] The study also showed significantly less ESBL contamination on free range chicken compared to conventional.

In Australia, where fluoroquinolones "have never been licensed for use in food production animals," a study observed fluoroquinolone-resistant bacteria in only a small number of human samples.[335] The study subjects who did carry fluoroquinolone-resistant bacteria appeared to have acquired the bacteria during overseas travel.[336]

Individual farms exhibit the same connection between decreased antibiotic use in agriculture and decreased resistance. A comparison of conventional poultry farms with poultry farms that had recently ceased using antibiotics and transitioned to organic practices found a significantly lower prevalence of antibiotic-resistant *Enterococcus* in litter, feed, and water samples from

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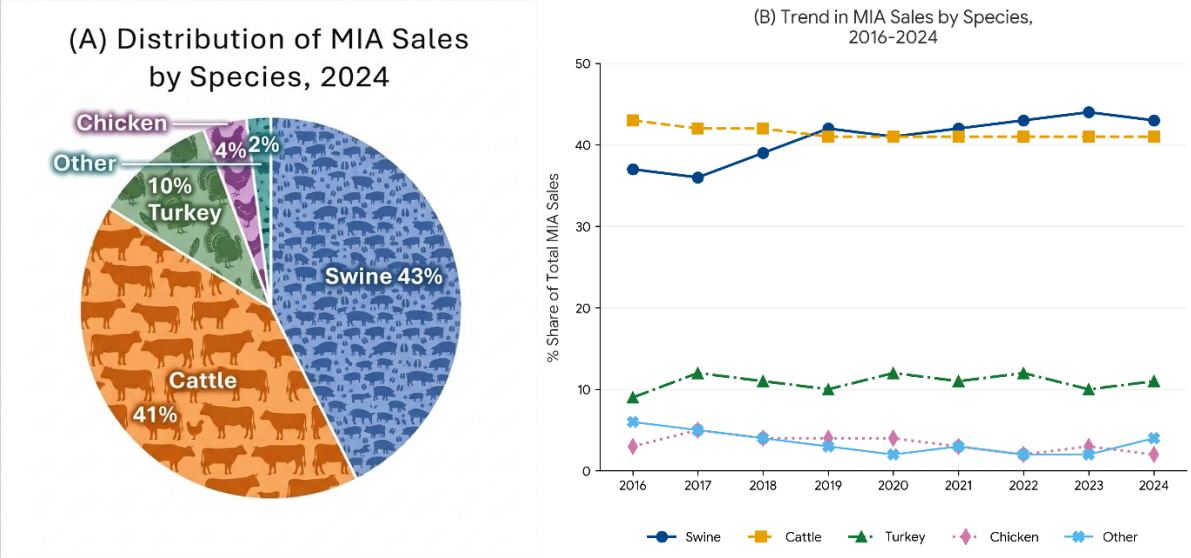
[328] Yvonne Agersø & Frank M. Aerstrup, *Voluntary Ban on Cephalosporin Use in Danish Pig Production Has Effectively Reduced Extended-Spectrum Cephalosporinase-Producing Escherichia coli in Slaughter Pigs*, 68 J. Antimicrobial Chemotherapy 569 (2013).
[329] *Id.*
[330] DANMAP, *DANMAP 2014: Use of Antimicrobial Agents and Occurrence of Antimicrobial Resistance in Bacteria from Food Animals, Food and Humans in Denmark* 16 (2014), https://www.food.dtu.dk/english/-/media/institutter/foedevareinstituttet/publikationer/pub-2015/rapport-danmap-2014.pdf.
[331] *Id.* at 19, 62.
[332] D.C. Speksnijder et al., *Reduction of Veterinary Antimicrobial Use in the Netherlands. The Dutch Success Model*, 62 Zoonoses & Pub. Health 79, 79, 84 (2015).
[333] Pepijn Huizinga et al., *Decreasing Prevalence of Contamination with Extended-Spectrum Beta-Lactamase-Producing Enterobacteriaceae (ESBL-E) in Retail Chicken Meat in the Netherlands*, 14 PLoS One (2019).
[334] *Id.*
[335] Leanne Unicomb et al., *Fluoroquinolone Resistance in Campylobacter Absent from Isolates, Australia*, 9 Emerging Infectious Diseases 1482, 1482 (2003).
[336] *Id.*

the farms no longer using antibiotics.[337] A 2026 meta-analysis comparing raised-without-antibiotics-farming with conventional farming found lower levels of resistance in farms without antibiotic use.[338]

Figure 11. U.S. Medically Important Antibiotic Sales by Animal Species: Distribution (2024) and Trend (2017–2024)[339]



Data comparing antibiotic use and antibiotic resistance in the U.S. show the same trend. As antibiotic use in poultry was reduced, more in response to consumer pressure than action by

[337] Amy R. Sapkota et al., *Lower Prevalence of Antibiotic-Resistant Enterococci on U.S. Conventional Poultry Farms that Transitioned to Organic Practices*, 119 Env't Health Persps. 1622 (2011).
[338] Asim Ur Rahman et al., *Comparative Analysis of Antibiotic-Administered vs. Antibiotic-Free Farming in Meat Production: Implications for Health, Environment, and Antibiotic Resistance*, 133 Food Microbiology (2026).
[339] Panel (A) shows the distribution of MIA sales across animal species in 2024. Panel (B) shows the trend in species share from 2017 to 2024.In January 2017, FDA's ban on antibiotics for growth promotion took effect. Compared to 2016, the chicken industry has reduced its MIA use by approximately 45%—demonstrating that meaningful reductions are achievable without harming production. By contrast, the swine industry increased its MIA use by approximately 50% in 2024 compared to 2017, and cattle use rose by approximately 25% in 2024 compared to 2017. These trends illustrate that voluntary stewardship has failed in the beef and pork sectors, which together represent the vast majority of agricultural antibiotic use. FDA, *2016 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals* 31 tbl. 2b (2017), https://www.fda.gov/files/about%20fda/published/2016-Summary-Report-on-Antimicrobials-Sold-or-Distributed-for-Use-in-Food-Producing-Animals.pdf; FDA, *2017 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals* 19 tbl. 4a (2018), https://www.fda.gov/media/119332/download; FDA, *2018 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals* 19 tbl. 4a (2019), https://www.fda.gov/media/133411/download; FDA, *2019 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals* 19 tbl. 4a (2020), https://www.fda.gov/media/144427/download; FDA, *2020 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals* 19 tbl. 4a (2021), https://www.fda.gov/media/154820/download; FDA, *2021 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals* 19 tbl. 4a (2022), https://www.fda.gov/media/163739/download?attachment; FDA, *2022 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals* tbl. 4a (2023), https://www.fda.gov/animal-veterinary/antimicrobial-resistance/2022-summary-report-antimicrobials-sold-or-distributed-use-food-producing-animals; FDA, *2023 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals* tbl. 4a (2024), https://www.fda.gov/animal-veterinary/antimicrobial-

FDA, there was a reduction in resistance in indicator bacteria. And conversely, when antibiotic use in the swine sector increased after 2017, so did resistance in indicator bacteria.[340]

The reductions in use must be sufficiently large. The U.S. data also suggest that the drop in antibiotics use in 2016-2017 was not large enough to dramatically reduce resistance in cattle and pigs, which is consistent with studies finding that measurable reductions in antibiotic resistance occur only if reductions in antibiotic use are large enough.[341] Similarly, a meta-analysis of studies looking at antibiotic use restrictions in food animals found that restrictions on continued use for prevention likely would have a similar impact on reducing resistance as a complete ban on the use of antibiotics, but that restricting a single class likely would have limited impact.[342]

Congress directed FDA to follow the science and ensure that drugs, including those used in food animal production, are safe for animals and humans. FDA must ensure a reasonable certainty of no harm from the intended uses. The science is clear that the current uses, challenged in this petition, do cause harm; there is and can be no dispute about this science. Moreover, the science is clear that FDA's partial, half-steps have not reduced use and exposure to safe levels. And further, the challenged uses are unnecessary for successful production of food animals. Fortunately, it is also clear that by eliminating the routine preventive use of antibiotics – and only by eliminating this use – FDA can significantly reduce harm and can achieve a "reasonable certainty of no harm." FDA must do so.

VII. SINCE THE SCIENCE IS CLEAR THAT LONGER ANTIBIOTIC USE INCREASES THE RISK OF ANTIBIOTIC RESISTANCE, FDA SHOULD SET STRICT DURATION LIMITS ON ANY ANIMAL USE

In addition to withdrawing approvals for the preventative use of antibiotics, there are additional steps needed to ensure that the use of antibiotics in food-producing animals is safe, as required by law. Because a major factor for the selection for resistance in bacteria from food animals is extent of use, as repeatedly acknowledged in FDA Guidance Documents, FDA should prohibit labeled durations of antibiotics that lead to high extent of use. Following FDA's own definition

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resistance/2023-summary-report-antimicrobials-sold-or-distributed-use-food-producing-animals; FDA, *2024 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals* tbl. 4a (2025), https://www.fda.gov/animal-veterinary/antimicrobial-resistance/2024-summary-report-antimicrobials-sold-or-distributed-use-food-producing-animals; Chris Dall, *FDA Report Shows Small Decline in Sales of Antibiotics for Food-Producing Animals*, CIDRAP (Oct. 15, 2024), https://www.cidrap.umn.edu/antimicrobial-stewardship/fda-report-shows-small-decline-sales-antibiotics-food-producing-animals; David Wallinga, NRDC, *U.S. Livestock Industries Persist in High-Intensity Antibiotic Use: Curbing Overuse Is Critical to Slow the Spread of Antibiotic Resistance* (2022), https://www.nrdc.org/sites/default/files/us-livestock-industries-persist-high-intensity-antibiotic-use-ib.pdf.

[340] Steve Roach, *FDA Policy Falls Short on Reducing Antibiotic Resistance*, Food Animal Concerns Trust, https://www.foodanimalconcernstrust.org/blog/fdapolicyfallsshort (last visited Apr. 7, 2026).

[341] Liton Chandra Deb, Manuel Jara & Cristina Lanzas, *Early Evaluation of the Food and Drug Administration (FDA) Guidance on Antimicrobial Use in Food Animals on Antimicrobial Resistance Trends Reported by the National Antimicrobial Resistance Monitoring System (2012–2019)*, 17 One Health (2023); Karen L. Tang et al., *Comparison of Different Approaches to Antibiotic Restriction in Food-Producing Animals: Stratified Results from a Systematic Review and Meta-Analysis*, 4 BMJ Glob. Health (2019).

[342] Karen L. Tang et al., *Comparison of Different Approaches to Antibiotic Restriction in Food-Producing Animals: Stratified Results from a Systematic Review and Meta-Analysis*, 4 BMJ Glob. Health (2019).

of high extent of use included in GFI #152, FDA should prohibit durations of use longer than 21 days and instead require a veterinarian to issue a new prescription if a longer duration of use is needed. Alternatively, FDA could prohibit continuous use—defined by FDA as over 14 consecutive days of antibiotic use. Growing evidence from human medicine shows that shorter durations of treatment are often as effective as long ones with lowered risk of antibiotic resistance and fewer other side effects.

a. Longer Duration Uses Are Not Safe.

Administering antibiotics for long periods of time increases exposure of bacteria to the antibiotic, increasing the risk that the bacteria will become resistant. Prolonged exposure of bacteria to the same antibiotic increases the likelihood of further adaptive mutations that make it easier for the resistant bacteria to continue to multiply and spread even when it is no longer exposed to the antibiotic;[343] and may also confer tolerance to higher antibiotic concentrations leading to resistant bacteria persisting longer in animals.[344] Many studies bear this out.[345] For example:

Multiple studies have looked at the use of tetracyclines in cattle. A series of studies looked at feeding chlortetracycline at a treatment dose to cattle for 23 days after administration by injection of another antibiotic ceftiofur. In these studies, chlortetracycline feeding led to a shift from pan-susceptible to multidrug resistant *Salmonella*, to persistence of cephalosporin resistance in *E. coli* during the feeding period, and to an increase in tetracycline resistance in bacteria isolated from feces.[346] Another feeding study found that the long-term use (over 60 days) of a combination of chlortetracycline and sulfamethazine at a dose (44 ppm) currently approved for "maintenance of weight gains" led to increases in resistance to both ampicillin and chlortetracycline in treated animals.[347] Long durations of use of chlortetracycline to control anaplasmosis have also led to increases in resistance in *E. coli*.[348]

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[343] Paulo Durão, Roberto Balbontín & Isabel Gordo, *Evolutionary Mechanisms Shaping the Maintenance of Antibiotic Resistance*, 26 Trends Microbiology 677 (2018).
[344] Erik Wistrand-Yuen et al., *Evolution of High-Level Resistance During Low-Level Antibiotic Exposure*, 9 Nature Commc'ns (2018).
[345] Studies also suggest the corollary is true: using antibiotics for shorter periods of time reduces both antibiotic resistance and other negative impacts, as indicated by numerous recent studies in human healthcare settings. *See* Antonio Vitiello et al., *The Importance of Antibiotic Treatment Duration in Antimicrobial Resistance*, 43 Eur. J. Clinical Microbiology & Infectious Diseases 1673 (2024); Ming Liu et al., *Shorter Versus Longer-Duration Antibiotic Treatments for Immunocompetent Patients with Bloodstream Infections: A Systematic Review and Meta-Analysis*, 86 EClinicalMedicine (2025); Brad Spellberg & Louis B. Rice, *Duration of Antibiotic Therapy: Shorter Is Better*, 171 Annals Internal Med. 210 (2019).
[346] *See* Naomi Ohta et al., *Population Dynamics of Enteric Salmonella in Response to Antimicrobial Use in Beef Feedlot Cattle*, 7 Sci. Reps. (2017); Neena Kanwar et al., *Effects of Ceftiofur and Chlortetracycline Treatment Strategies on Antimicrobial Susceptibility and on tet(A), tet(B), and bla$_{CMY-2}$ Resistance Genes Among E. coli Isolated from the Feces of Feedlot Cattle*, 8 PloS One (2013) (on *E. coli*); Margaret D. Weinroth et al., *Effects of Ceftiofur and Chlortetracycline on the Resistomes of Feedlot Cattle*, 84 Applied & Env't Microbiology (2018) (on the abundance of tetracyline resistance genes).
[347] T.W. Alexander et al., *Effect of Subtherapeutic Administration of Antibiotics on the Prevalence of Antibiotic-Resistant Escherichia Coli Bacteria in Feedlot Cattle*, 74 Applied & Env't Microbiology 4405 (2008).
[348] Naemi Pomwenepawa Bickmeier, *Shifts in the Antibiotic Susceptibility Profiles of Zoonotic Enteric Bacteria in Response to Long-Term Chlortetracycline Usage for the Control of Bovine Anaplasmosis* (2025) (Ph.D. dissertation, Kansas State University) (ProQuest).

Studies of long duration chlortetracycline use in pigs have found similar results. One compared chlortetracycline in feed at a treatment dose for a short duration, with a growth promotion dose for a long duration and found chlortetracycline resistance increased in coliform bacteria from the long duration use.[349] Another looked at chlortetracycline for long-term use in swine at 50g/ton, which is within the dose range for disease prevention in swine, and found increased resistance to multiple antibiotics when compared to pigs not fed chlortetracycline.[350] A third study found feeding a treatment dose of chlortetracycline to pigs for 42 days increased resistance to tetracyclines and cephalosporins in pigs.[351]

Studies of long duration use of the macrolide antibiotic tylosin have also been shown to increase resistance in bacteria selected from food-producing animals. One showed that using tylosin in cattle at the prevention dose led to increased resistance to erythromycin in enterococcus over the period of the study.[352] A systematic review and semi-quantitative analysis of studies looking at long-term use of tylosin in feedlot cattle and found that this use increases the resistance to macrolide antibiotics of enterococci in the gut of cattle.[353] A third study found long duration use of tylosin in pig feed led to resistance that persisted through slaughter despite a withdrawal period where antibiotics were not fed.[354] A fourth found that a low-dose, long duration administration of tylosin in the water of chickens led to increased macrolide resistance compared to a short, high-dose administration.[355] A fifth study showed that long duration use of the streptogramin antibiotic virginiamycin led to increased resistance to the drug class in enterococci from animals fed the antibiotic.[356]

While there are also studies indicating that long term use of antibiotics in the feed or water of food-producing animals does not lead to resistance, these should be viewed with appropriate skepticism. For example, one study looked at the administration of the antibiotics tiamulin and chlortetracycline in either water or feed on resistance in pigs and found no impact.[357] But it is

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[349] B. E. Langlois et al., *Antibiotic Resistance of Fecal Coliforms from Swine Fed Subtherapeutic and Therapeutic Levels of Chlortetracycline*, 58 J. Animal Sci. 666 (1984).

[350] *See* Julie A. Funk et al., *The Effect of Subtherapeutic Chlortetracycline on Antimicrobial Resistance in the Fecal Flora of Swine*, 12 Microbial Drug Resistance 210 (2006). 50g/ton is within the dosage rage for the prevention indication for "reducing the incidence of cervical lymphadenitis (jowl abscesses)" under 21 C.F.R. § 558.128 (e)(3)(i).

[351] Hayden E. Williams et al., *Effects of Chlortetracycline Alone or in Combination with Direct Fed Microbials on Nursery Pig Growth Performance and Antimicrobial Resistance of Fecal Escherichia coli*, 96 J. Animal Sci. 5166 (2018).

[352] *See* Rahat Zaheer et al., *Effect of Subtherapeutic vs. Therapeutic Administration of Macrolides on Antimicrobial Resistance in Mannheimia haemolytica and Enterococci Isolated from Beef Cattle*, 4 Frontiers in Microbiology (2013). The dose in the study is 11 ppm, which is approximately the same as the 10 g/ton approved for reduction of infection by liver abscesses challenged by this petition, 21 C.F.R. § 558.625(e)(2)(1).

[353] Casey L. Cazer et al., *The Effect of Tylosin on Antimicrobial Resistance in Beef Cattle Enteric Bacteria: A Systematic Review and Meta-Analysis*, 176 Preventive Veterinary Med. (2020).

[354] Devin B. Holman & Martin R. Chénier, *Impact of Subtherapeutic Administration of Tylosin and Chlortetracycline on Antimicrobial Resistance in Farrow-to-Finish Swine*, 85 FEMS Microbiology Ecology 1 (2013).

[355] Scott R. Ladely et al., *Development of Macrolide-Resistant Campylobacter in Broilers Administered Subtherapeutic or Therapeutic Concentrations of Tylosin*, 70 J. Food Prot. 1945 (2007).

[356] Patrick F. McDermott et al., *Changes in Antimicrobial Susceptibility of Native Enterococcus faecium in Chickens Fed Virginiamycin*, 71 Applied & Env't Microbiology 4986 (2005).

[357] Victor L. Ishengoma et al., *The Impact of In-Water vs. In-Feed Chlortetracycline and Tiamulin Administration in Piglets on the Fecal Prevalence and Antimicrobial Resistance of Salmonella*, 4 Applied Microbiology 297 (2024).

reasonable to assume that this was because the animals rapidly became infected with a strain of *Salmonella* resistant to both tested drugs, indicating that preexisting resistance in the livestock raising system likely masked the impact of current antibiotic use.[358] After decades of antibiotic use in agricultural settings, resistance in the food-animal production environment can make it difficult to see the impact of changes in antibiotic use.[359]

FDA itself appeared to recognize the risks associated with long duration use of antibiotics, as is apparent in its now-rescinded regulation requiring studies for the administration of antibiotics for more than 14 days,[360] and its recommendation that high or medium risk antibiotics not be administered to groups of animals for more than 21 days.[361]

FDA has never shown the use of MIAs in livestock and poultry for more than 21 days to be safe. FDA issued all of these approvals without requiring adherence to GFI #152's risk assessment approach for evaluating the safety risks posed by antimicrobial new animal drugs (either before GFI #152 or ignoring its mandates).[362]

b. Rather than Regulating Antibiotics to Prevent Dangerous Long Duration Use in Livestock and Poultry, FDA is Watering Down its Guidance on Duration of Use.

After the publication of GFI #213 in 2013, FDA again emphasized that prolonged use of MIAs in food-producing animals poses a risk to human health. This restatement underscored the rationale behind earlier measures—such as requiring resistance testing for uses longer than 14 days and setting a 21-day limit under GFI #152—and invited comment on applying duration limits to MIAs without existing restrictions.[363] In 2023, FDA released Draft GFI #273 "Defining

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[358] *Cf.* Neena Kanwar et al., *Effects of Ceftiofur and Chlortetracycline Treatment Strategies on Antimicrobial Susceptibility and on tet(A), tet(B), and bla$_{CMY-2}$ Resistance Genes Among E. coli Isolated from the Feces of Feedlot Cattle*, 8 PloS One (2013); Catrione Lee et al., *Effect of Antimicrobial Use in Conventional Versus Natural Cattle Feedlots on the Microbiome and Resistome*, 11 Microorganisms (2023).

[359] Enrique Doster et al., *Evaluating the Effects of Antimicrobial Drug Use on the Ecology of Antimicrobial Resistance and Microbial Community Structure in Beef Feedlot Cattle*, 13 Frontiers Microbiology (2022). Studies have shown resistance can continue to decline on farms years after antibiotics are completely withdrawn, illustrating the role of long-term antibiotic use on resistance. *See* Susan N. Rollo et al., *Prevalence and Patterns of Antimicrobial Resistance in Campylobacter spp Isolated from Pigs Reared Under Antimicrobial-Free and Conventional Production Methods in Eight States in the Midwestern United States*, 236 J. Am. Veterinary Med. Ass'n 201 (2010); *see also* Getahun E. Agga et al., *Persistence of Antibiotic Resistance Genes in Beef Cattle Backgrounding Environment over Two Years After Cessation of Operation*, 14 PLOS ONE (2019). For cattle feedlots, the circulation of bacteria, including pathogens, between animals and pens is very high, making it difficult to detect difference across treatments. *See* Osman Y. Koyun, *Disease Occurrence In- and the Transferal of Zoonotic Agents by North American Feedlot Cattle*, 12 Foods 904 (2023). These differences are evident when comparing feedlots that use antibiotics with those that do not; however, resistance persists even in facilities where antibiotics are not used. *See* Catrione Lee et al., *Effect of Antimicrobial Use in Conventional Versus Natural Cattle Feedlots on the Microbiome and Resistome*, 11 Microorganisms (2023).

[360] J.M. Gilbert, *A Review of Studies Submitted to CVM Assessing the Effects of Sub-Therapeutic Use of Antimicrobial Drugs on the Salmonella Reservoir in Food Producing Animals* 2 (2001). Attached as Appendix B.

[361] Original GFI #152 at 23 tbl. 7, 25 tbl. 8.

[362] J.M. Gilbert, *A Review of Studies Submitted to CVM Assessing the Effects of Sub-Therapeutic Use of Antimicrobial Drugs on the Salmonella Reservoir in Food Producing Animals* 7 (2001). Attached as Appendix B.

[363] The Judicious Use of Medically Important Antimicrobial Drugs in Food- Producing Animals; Establishing Appropriate Durations of Therapeutic Administration; Request for Comments, 81 Fed. Reg. 63187, 63187 (Sep. 14, 2016).

Durations of Use for Approved Medically Important Antimicrobial Drugs Fed to Food-Producing Animals" that lays out a voluntary process for drug sponsors to add durations for approved MIAs that do not have a duration of use.[364]

Unlike the regulatory approach which had a 14-day limit or GFI #152 with its 21-day limit for high or medium risk uses, GFI #273 asks sponsors to select a duration based on the "range of legitimate circumstances or scenarios that may occasionally be encountered in the United States."[365] This approach shifts decision-making around drug use from setting durations short enough to protect human health—as required under prior regulations and GFI #152—to allowing durations based solely on the opinion or judgment of the drug sponsor, without any required consideration of human health impacts or the potential for resistance in animals. While the goal of GFI #273 claims to be minimizing resistance,[366] drug makers are not asked to consider resistance at all in setting the appropriately targeted durations. FDA merely states that "it will be difficult to justify a proposed maximum permitted duration of use that approaches either the production lifespan of the target animal or the maximum VFD expiration date" but that for some indications "there likely are scenarios in which it will be necessary and consistent with the principles of judicious use to feed the drug for an extended period."[367]

This rationale simply ignores the real problem. In human medicine, there is a growing recognition that shorter durations of use are an important tool for stewardship and also reduce the risk of other negative side-effects of antibiotic use—though in these human cases the long durations are two weeks or shorter.[368] There is no justification for ignoring that science here.

VIII. CURRENT DATA COLLECTION EFFORTS ARE INADEQUATE AND FDA SHOULD COLLECT SPECIES- AND PURPOSE-SPECIFIC USE DATA

Since at least 2001, federal health authorities have recognized the need to collect data on how and why antibiotics are used on farms. The 2001 Public Health Action Plan of the Interagency Task Force on Antimicrobial Resistance, created by federal agencies (including FDA) to better address the growing threat of antimicrobial resistance, included antibiotic use data collection as a priority action item.[369] The collection of species-specific drug use data is also recommended by WHO,[370] Food and Agriculture Organization (FAO), Codex Alimentarius, and the World

[364] Defining Durations of Use for Approved Medically Important Antimicrobial Drugs Fed to Food- Producing Animals; Draft Guidance for Industry; Availability, 88 Fed. Reg. 66009, 66009 (Sep. 26, 2023).
[365] GFI #273 at 15.
[366] *Id.* at 1
[367] *Id.* at 15.
[368] Brad Spellberg & Louis B. Rice, *Duration of Antibiotic Therapy: Shorter Is Better*, 171 Annals of Internal Med. 210 (2019).
[369] *See* Interagency Task Force on Antimicrobial Resistance, *A Public Health Action Plan to Combat Antimicrobial Resistance Part 1: Domestic Issues* 2–3 (2001), https://stacks.cdc.gov/view/cdc/6665.
[370] WHO, *WHO Global Principles for the Containment of Antimicrobial Resistance in Animals Intended for Food* 6 (2000), https://iris.who.int/server/api/core/bitstreams/9b39a179-0a0d-4021-be65-9d0308ed8566/content; WHO, *Integrated Surveillance of Antimicrobial Resistance: Guidance from a WHO Advisory Group* 27 (2013), https://iris.who.int/server/api/core/bitstreams/76610579-5ccf-4f7d-991d-cc550e979df5/content; WHO, *Integrated Surveillance of Antimicrobial Resistance in Foodborne Bacteria: Application of a One Health Approach* 37–38 (2017), https://iris.who.int/server/api/core/bitstreams/9ab8affe-760a-4f4b-b166-52b0b9ace0ef/content.

Organization for Animal Health (WOAH, formerly OIE).[371] In two reviews of the National Antimicrobial Resistance Monitoring System (NARMS), FDA's Science Advisory Board recommended that drug use data be integrated with microbiological data, and one stated that the lack of drug use data "represents a critical barrier for NARMS to achieve its objectives and further utility."[372] The collection of data on antibiotic use in food-producing animals is included in the U.S. National Action Plan to Combat Antibiotic Resistant Bacteria[373] and in FDA's current five-year plan to combat antibiotic resistance.[374]

Notwithstanding this mountain of recommendations for detailed reporting, the only comprehensive national level data on antibiotic use in food-producing animals currently available is national sales data reported by drug makers as required by Congress in Section 105 of the 2008 Animal Drug User Fee Reauthorization.[375] These sales data are available for years between 2009 and 2024. In 2015, FDA began requiring drug sponsors to estimate use by animal species.[376] Prior to this, the only data reported was volume of sales by drug class and by route of administration. Because most drugs are approved for multiple indications, the sales data do not provide information on reason of use or even information on type of use (i.e., growth promotion, disease prevention, disease control, or treatment).[377] In addition, it is not clear how accurate the species-specific estimates are since FDA does not mandate a method to be used in determining them.[378]

FDA has acknowledged that better data on antibiotic use in agriculture is needed to measure the impact of and to improve efforts to control antibiotic resistance and to better understand the association between use and resistance.[379] FDA also needs better data on how antibiotics are used, to inform "regulatory policies to help slow the development of antibiotic resistance."[380] The importance of better data is clearly illustrated by FDA's inability to explain the large jump

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[371] World Org. for Animal Health, *Monitoring Of the Quantities and Usage Patterns of Antimicrobial Agents Used in Food Producing Animals*, *in Terrestrial Animal Health Code* (2018), https://www.woah.org/fileadmin/Home/eng/Health_standards/tahc/2018/en_chapitre_antibio_monitoring.htm#:~:text=Chapter%206.9%20of%20the%20Terrestrial%20Code%20describes,efforts%20to%20ensure%20responsible%20and%20prudent%20use.

[372] *See* FDA Sci. Advisory Bd. External Subcomm., *National Antimicrobial Resistance Monitoring System (NARMS) Program Review* 4 (2007), http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4329b_02_06_NARMS%20Review%20Update.pdf; FDA, *Science Board Review of the National Antimicrobial Resistance Monitoring System* 6–7 (2017), https://www.fda.gov/media/105455/download.

[373] Fed. Task Force on Combating Antibiotic-Resistant Bacteria, *National Action Plan for Combating Antibiotic-Resistant Bacteria 2020-2025*, at 28 (2020), https://aspe.hhs.gov/sites/default/files/migrated_legacy_files/196436/CARB-National-Action-Plan-2020-2025.pdf.

[374] FDA, Supporting Antimicrobial Stewardship in Veterinary Settings Goals for Fiscal Years 2024-2028: Key Phase 3 and Phase 4 Actions, at 12 (2023), https://www.fda.gov/media/172347/download?attachment.

[375] Animal Drug User Fee Amendments of 2008, Pub. L. No. 110–316, § 105, 122 Stat. 3509, 3513–14 (2008).

[376] Antimicrobial Animal Drug Sales and Distribution Reporting, 81 Fed Reg. 29129, 29129 (May 11, 2016).

[377] *Questions and Answers: Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals*, FDA, https://www.fda.gov/industry/animal-drug-user-fee-act-adufa/questions-and-answers-summary-report-antimicrobials-sold-or-distributed-use-food-producing-animals#use (last updated Dec. 8, 2025).

[378] Antimicrobial Animal Drug Sales and Distribution Reporting, 81 Fed Reg at 29141.

[379] Collecting On-Farm Antimicrobial Use and Resistance Data; Public Meeting; Request for Comments, 80 Fed. Reg. 50638, 50638 (Aug. 20, 2015).

[380] *Data on Antimicrobial Use in Animals*, FDA, https://www.fda.gov/animal-veterinary/antimicrobial-resistance/data-antimicrobial-use-animals (last updated Sep. 30, 2025).

in antibiotic use between 2023 and 2024.[381] The current data shows a rise but provides no information on why it occurred and thus does not provide information on how to better manage use to keep future large rises in use from reoccurring.

In 2015, FDA announced it was working in collaboration with the U.S. Department of Agriculture and CDC, and held a public meeting "on possible approaches for collecting additional on-farm antimicrobial drug use and resistance data" in order to "assess[] the impact" of FDA's efforts at that time to combat antibiotic resistance under GFI #213.[382] Now, more than ten years later and six years after GFI #213 has been fully implemented, there still is no data collection system in place.

FDA in recent years has shifted the focus of its plans for antibiotic use data collection to a voluntary public private partnership approach, through collaboration with the Reagan-Udall Foundation. In advancing this approach, FDA has disregarded requests to evaluate alternative options and has overlooked significant concerns regarding the representativeness of a voluntary program. At this time, FDA's public private partnership is nothing more than a draft framework. It is not a viable program.

With some effort, FDA should be able to collect a far more useful data set using records kept by feed mills. Feed mills are required under existing regulations to keep manufacturing and distribution records for all livestock and poultry feed containing MIAs and to make them available to FDA for inspection.[383] In addition, feed mills are required to have a written order from a veterinarian, called a Veterinary Feed Directive or VFD, before distributing any feed containing a medically important antibiotic to a livestock producer.[384] The VFD includes information on the animals, the drug dose, and the specific indication for which the antibiotic is being fed.[385] The combination of feed distribution records (exactly what amount of feed and quantity of antibiotic) along with the veterinary order which describes indication, species, and livestock sector could provide data on the amount of antibiotic, animal species and sector receiving the antibiotic, and reason for use. If manufacturing records and VFDs were collected, this would provide needed data on the 65% of medically important antibiotics administered in feed.[386] FDA should use its existing authority to begin collecting, analyzing, and publicly reporting this data. While collection of this data does not cover all antibiotics used in food-producing animals, this collection can be done using existing authorities and avoids many of the limitations of the national sales data currently collected and the voluntary approach to data

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[381] *FDA Releases Annual Summary of Sales and Distribution of Antimicrobials in 2024 for Use in Food-Producing Animals*, FDA, https://www.fda.gov/animal-veterinary/cvm-updates/fda-releases-annual-summary-sales-and-distribution-antimicrobials-2024-use-food-producing-animals (last updated Dec. 5, 2025).
[382] Collecting On-Farm Antimicrobial Use and Resistance Data, 80 Fed. Reg. at 50638.
[383] Since the implementation of GFI #213 in 2017, all MIAs administered in feed to food-producing animals require a veterinarian's order, which for feed is called a Veterinary Feed Directive. 21 C.F.R. § 558.6(c) describes record keeping requirements for manufacturers and distributers of MIAs in feed in sections (3) and (4).
[384] 21 C.F.R. § 558.6(c)(1) (2025).
[385] *Id.* § 555.6 (b)(3).
[386] FDA, *2023 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals* tbl. 6b (2024), https://www.fda.gov/animal-veterinary/antimicrobial-resistance/2023-summary-report-antimicrobials-sold-or-distributed-use-food-producing-animals.

collection being explored by FDA. This additional data could complement any other voluntary data FDA collects.

IX. FDA SHOULD SET ANIMAL-SECTOR-SPECIFIC REDCUTION TARGETS AS TOOLS FOR COMBATTING ANTIBIOTICS RESISTANCE

Finally, FDA should set public health goals for reductions in antibiotic use by animal species and sector. These are needed to set expectations for the regulated industry and to provide accountability for FDA around its efforts to ensure the safety of antibiotics used in food-producing animals. While FDA does not have explicit authority to set antibiotic use reduction targets it could do this in the form of a guidance document which by definition does not create legal obligations, but instead covers its current thinking on a topic. The value of an antibiotic reduction target like other public health goals is not in its enforceability, but as a goal that is considered necessary to be met.

Given that antibiotic use is the main driver of antibiotic resistance, reducing antibiotic use is a primary mechanism for combating antibiotic resistance. Programs that promote stewardship or judicious use that do not result in reduced use are unlikely to have much impact on resistance. Reductions in overall use can occur both as a result of decreased overuse or misuse, or as a byproduct of improved infection prevention and control measures. Both will decrease the amount of antibiotics used. Because of the importance of reducing antibiotic use for effectively controlling antibiotic resistance, global leaders—including the U.S.—in 2024 signed a declaration to meaningfully reduce the amount of antibiotics used in agriculture by 2030.[387]

Metrics are needed to measure the impact of efforts to combat antibiotic resistance with measures of antibiotic use and number of resistant infections holding particular importance. In the U.S., CDC has set targets for reductions in antibiotic use in both hospitals and out-patient settings.[388] It would be reasonable to do the same for antibiotic use in animals.

FDA, which has authority over the safety of antibiotics used in animals, has not set any antibiotic use reduction targets and does not include the phrase "reduce antibiotic use" in its discussion of antibiotic resistance. Rather, FDA uses "reduce the need" for antibiotics, effectively presuming that all current use is in fact needed.[389] France[390] and the Netherlands[391] have successfully used targets for the reduction of antibiotic use in food producing animals as a tool in their efforts to combat antibiotic resistance. FDA should set livestock sector reduction targets for antibiotic use. Sector specific targets are needed because of the large variation in use across sectors.

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[387] United Nations, *Political Declaration of the High-Level Meeting on Antimicrobial Resistance* 10 (2024), https://www.un.org/pga/wp-content/uploads/sites/108/2024/09/FINAL-Text-AMR-to-PGA.pdf.
[388] *Antibiotic Use in the United States, 2021 Update: Progress and Opportunities*, CDC, https://archive.cdc.gov/www_cdc_gov/antibiotic-use/stewardship-report/2021.html (last updated Oct. 6, 2022).
[389] FDA, *Antimicrobial Use and Resistance in Animal Agriculture in the United States 2016-2019*, at 87, 115, 141–42, 165 (2022), https://www.fda.gov/media/159544/download.
[390] Elissa Khamisse et al., *Rethinking the Role of Animals in Antimicrobial Resistance*, 7 Lancet Microbe (2026).
[391] D.C. Speksnijder et al., *Reduction of Veterinary Antimicrobial Use in the Netherlands. The Dutch Success Model*, 62 Zoonoses Pub. Health 79 (2015).

X. CONCLUSION

For over 50 years, FDA has known that the extensive use of antibiotics in food-producing animals selects for resistance to these drugs in bacteria in the animals receiving them and that this resistance negatively impacts human health. Despite FDA's legal obligation to ensure the safety of drugs used in animal agriculture, FDA has never adequately addressed the threat. In fact, FDA has watered down its guidance instead of tightening its regulations.

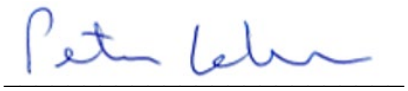
FDA must comply with its legal duty to withdraw approval for animal drug uses that are not shown to be safe for human health. We request that FDA find the use of medically important antibiotics in the feed and water of food-producing animals for long durations or for purposes other than treatment and control of infection in animals with diagnosed illness are unsafe and that the agency withdraws approval for such uses. In addition, we request that FDA begin collecting, analyzing, and reporting data from distributors of medicated feed containing MIAs and set sector specific targets for antibiotic use reductions. These steps are all needed to ensure the safety of antibiotics used in food-producing animals.

C. Environmental Impact

FDA's regulations indicate that the action requested is among the class of actions that are "categorically excluded and, therefore, ordinarily do not require the preparation of an [Environmental Assessment] or an [Environmental Impact Statement]." 21 C.F.R. § 25.33 & subsection (g).

D. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.



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Alliance for Humane Biotechnology

Alliance of Nurses for Healthy Environments

American Regeneration

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Anura Capital

Beyond Pesticides

Buffalo River Watershed Alliance

Center for Biological Diversity

Center for Food Safety

Committee on the Middle Fork Vermilion River

Compassion in World Farming

Consumer Reports

California Rural Legal Assistance Foundation

Cultivate Charlottesville

Delaware Riverkeeper Network

Farm Forward

Farm Sanctuary

FarmSTAND

Farmworker and Landscaper Advocacy Project

Farmworker Association of Florida

Food & Water Watch

Food Animal Concerns Trust

Foodwise

FOUR PAWS

Friends of the Earth

Public Citizen

Green America

HEAL (Health, Environment, Agriculture, Labor) Food Alliance

Health Care Without Harm

Hudson Riverkeeper

Jefferson County Farmers & Neighbors, Inc.

Latino Farmers & Ranchers International, Inc.

Lymphoma Foundation of America

Mercy For Animals

Minnesota Center for Environmental Advocacy

Northeast Organic Farming Association of New York

Nutrient Density Initiative

Pasa Sustainable Agriculture

Pediatric Infectious Diseases Society

Pesticide Action and Agroecology Network

Regenerative Agriculture Coalition

Rural Coalition

Science and Environmental Health Network

Sierra Club

Socially Responsible Agriculture Project

Soul Fire Farm

The Non-GMO Project / Food Integrity Collective

Unitarian Universalist Animal Ministry

United We Eat

Urban Tilth

Western Nebraska Resources Council

Women’s International League for Peace and Freedom, U.S. Section

Waterkeeper Alliance

National Consumers League

Environmental Working Group

Farm Aid

Moms Across America

Non-Toxic Neighborhoods

Northeast Organic Farming Association of New Hampshire

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