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CITIZEN PETITION

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 submit this petition under section 512(e) of the Food, Drug, and Cosmetic Act, 21 U.S.C. § 360b(e), to request that the Commissioner of Food and Drugs withdraw approval of the use of medically important antibiotics in livestock and poultry for disease-prevention or growth-promotion purposes.

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ACTION REQUESTED

The Natural Resources Defense Council (NRDC),¹ Center for Science in the Public Interest (CSPI),² Earthjustice,³ Food Animal Concerns Trust (FACT),⁴ Public Citizen,⁵ U.S. Public Interest Research Group (U.S. PIRG),⁶ and California Public Interest

¹ NRDC is a nonprofit environmental and public health advocacy organization headquartered in New York, New York, with a national membership of more than 298,000. Among other activities, NRDC engages in research, advocacy, and litigation to improve the regulation of harmful substances in food and consumer products, including drug-resistant bacteria engendered by the misuse and overuse of antibiotics and other antibacterial products.

² CSPI is a science-based nonprofit organization that focuses on nutrition and food safety issues. It is based in Washington, DC. CSPI is supported by about 610,000 American subscribers-members. For more than a decade, CSPI has published reports and articles about the risks of antibiotic use in farm animals.

³ Based in San Francisco, Earthjustice is the country's largest nonprofit public interest environmental law organization and has represented more than 1,000 public interest clients since its founding in 1971. We wield the power of law and the strength of partnerships to protect people's health, preserve wild places and wildlife, advance clean energy, and combat climate change, including seeking strategies to reduce the health, environmental, and climate harms from the production of our food and to promote a more environmentally sound agricultural system.

⁴ FACT is a national, nonprofit organization located in Chicago, Illinois, that promotes the humane and safe production of meat, milk, and eggs. Eliminating the overuse of medically important antibiotics in livestock has been one of FACT's top priorities for almost two decades.

⁵ Founded in 1971, Public Citizen is a national, nonprofit, public interest organization, headquartered in Washington, DC, with members and supporters nationwide. Public Citizen works before Congress, regulatory agencies, and in the courts to advance consumer interests on a wide range of issues, including healthcare policy and drug safety.

⁶ U.S. PIRG, a federation of state PIRG organizations, stands up to special interests on behalf of the American public, working to win concrete results for the public's health and well-being. With members throughout the country, U.S. PIRG is a non-profit, non-partisan organization that works on issues such as product safety, public health, campaign finance reform, and consumer protection.

Research Group, Inc. (CALPIRG),⁷ hereby petition the Commissioner of Food and Drugs to withdraw approval of the use of the following medically important antibiotics in livestock and poultry for disease-prevention⁸ or growth-promotion purposes:

1. macrolides
2. lincosamides
3. penicillins
4. streptogramins
5. tetracyclines
6. aminoglycosides
7. sulfonamides⁹

⁷ CALPIRG takes action when consumers are cheated or the voices of ordinary citizens are drowned out by special interests. Using the tools of investigative research, media exposés, grassroots organizing, advocacy, and litigation, CALPIRG protects consumers, encourages a fair, sustainable economy, and fosters responsive, democratic government. CALPIRG is a nonprofit, nonpartisan organization with members throughout California.

⁸ The Food and Drug Administration (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.” FDA, Guidance for Industry No. 209, The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals 21 n.5 (Apr. 13, 2012), <http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM216936.pdf> [hereinafter Guidance No. 209]. 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.

⁹ See NRDC Fact Sheet, FDA’s Efforts Fail to End Misuse of Livestock Antibiotics 4 (2015), <https://www.nrdc.org/resources/fdas-efforts-fail-end-misuse-livestock-antibiotics> (listing medically important antibiotics still approved for routine use in livestock); FDA, Guidance for Industry No. 152, Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern, App. A (Oct. 23, 2003), <http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm052519.pdf> (classifying antibiotics according to their importance to human medicine) [hereinafter Guidance No. 152]; FDA, Approved Animal Drug Products Online (Green Book), updated January 2015, <http://www.fda.gov/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/default.htm> (accessed July 15, 2016). The appendix to

Petitioners submit this petition pursuant to 21 C.F.R. § 10.25(a) and section 512(e) of the Food, Drug, and Cosmetic Act, 21 U.S.C. § 360b(e).

Withdrawal proceedings are required because the scientific evidence demonstrates that the use of these antibiotics for growth-promotion and disease-prevention purposes in livestock¹⁰ production is not shown to be safe for human health.¹¹

STATEMENT OF GROUNDS

I. Introduction

Public health authorities, including FDA, have known for decades that the use of antibiotics in livestock production contributes to the development and proliferation of antibiotic-resistant bacteria. In the last decade, scientific studies have confirmed that: bacteria exposed to livestock antibiotics develop mutations or acquire genes that make them resistant to antibiotics and in some cases more likely to cause disease; bacteria that carry resistance genes can transfer those genes to other, non-resistant bacteria; people who live near or come into contact with farm facilities are more likely to carry antibiotic-resistant bacteria and develop antibiotic-resistant infections; and the use of antibiotics in livestock increases the prevalence of resistant bacteria in the environment and the general human population.

FDA, which regulates the use of antibiotics in livestock, is required to withdraw its approval of animal drug uses that are “not shown to be safe” for human health.¹² The scientific evidence demonstrates that the routine use of medically important antibiotics to promote animal growth and prevent disease is not shown to be safe. Although all antibiotic use contributes to antibiotic resistance, growth-promotion and disease-prevention uses are especially pernicious. These uses involve the administration of low doses of antibiotics to large groups of animals over long periods of time, conditions that

this petition includes all references cited, with the exception of some publicly available documents not required by FDA’s regulations to be included. *See* 21 C.F.R. § 10.20(c)(1).

¹⁰ “Livestock” as used in this petition includes poultry.

¹¹ *See* 21 U.S.C. § 360b(e)(1)(B).

¹² 21 U.S.C. § 360b(e)(1)(B); *id.* § 321(u) (defining “safe”).

pose a higher risk of promoting resistance than short-term treatment doses to individual animals.¹³

Rather than ban the use of medically important antibiotics for growth-promotion or disease-prevention purposes, however, FDA has adopted a voluntary program that disapproves only of growth-promotion uses. FDA's Guidance No. 213, which describes the agency's voluntary program, condones the use of antibiotics for disease prevention¹⁴—in other words, to compensate for the stressful, crowded, and unsanitary conditions that are common in livestock-production facilities.¹⁵ Disease prevention, however, accounts for a significant fraction of antibiotic use: both FDA and industry spokespeople now estimate that growth-promotion uses constitute only 10-15 percent of total use.¹⁶ Thus, by allowing the continued use of antibiotics for disease prevention, FDA's voluntary program will fail to reduce livestock antibiotic use significantly, even if members of industry choose to participate in the program. Moreover, because

¹³ See Environmental Defense et al., Citizen Petition Seeking Withdrawal of Approvals of Certain Herdwide / Flockwide Uses of Critically Important and Highly Important Antibiotics Pursuant to Guidance #152, FDA Docket No. 2005P-0139/CP 1, at 11 (Apr. 8, 2005) (demonstrating that, based on FDA's own risk-assessment method, described in Guidance No. 152, herd-wide and flock-wide uses of medically important antibiotics present unacceptably high levels of risk); NRDC, *Playing Chicken with Antibiotics* 6 (Jan. 2014), <https://www.nrdc.org/sites/default/files/antibiotic-feed-fda-documents-IB.pdf> (reporting FDA's conclusions that certain animal feed products containing tetracyclines, penicillins, aminoglycosides, and/or sulfonamides are "high risk" and therefore, under Guidance No. 152, should not be administered to large groups of animals over long periods of time).

¹⁴ FDA, *Guidance for Industry No. 213, New Animal Drugs and New Animal Drug Combination Products Administered in or on Medicated Feed or Drinking Water of Food-Producing Animals: Recommendations for Drug Sponsors for Voluntarily Aligning Product Use Conditions with GFI No. 209*, at 6-7 (Dec. 2013), <http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM299624.pdf> [hereinafter *Guidance No. 213*].

¹⁵ See NRDC Fact Sheet, *FDA's Efforts Fail to End Misuse of Livestock Antibiotics 2*, <https://www.nrdc.org/sites/default/files/fda-guidance-213.pdf>.

¹⁶ Beth Hoffman, *New FDA "Rules" Not Likely to Reduce Antibiotic Use on Farm*, *Forbes* (Dec. 13, 2013), <http://www.forbes.com/sites/bethhoffman/2013/12/13/new-fda-rules-will-not-reduce-antibiotic-use-on-farm/#5c4541e762dd>. William Flynn, the Deputy Director for Science Policy for FDA's Center for Veterinary Medicine, provided this estimate at a hearing of the Maryland General Assembly on November 2, 2015.

growth-promotion and disease-prevention doses are similar, Guidance No. 213 will allow livestock producers to continue using antibiotics for growth-promotion purposes, under the rubric of disease prevention.

Given that FDA's voluntary program allows the use of antibiotics for disease prevention to continue, it is unsurprising that there is no evidence to date that the voluntary program is reducing antibiotic use. Since 2013, when FDA's program began, antibiotic use in livestock has not decreased but *increased*. Use of medically important antibiotics in livestock increased by 3 percent in 2014 alone.¹⁷ Indeed, the data suggest that increases in antibiotic use are outpacing increases in livestock production, and that, on average, producers are using more drugs per animal than they did just a few years ago.¹⁸

The use of medically important antibiotics in livestock production for growth-promotion or disease-prevention purposes is not shown to be safe. FDA's voluntary program will not end these drug uses. FDA must immediately begin proceedings to withdraw approval for these uses.¹⁹

¹⁷ FDA, 2014 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals 40 (Dec. 2015), <http://www.fda.gov/downloads/ForIndustry/UserFees/AnimalDrugUserFeeActADUFA/UCM476258.pdf> [hereinafter 2014 use report].

¹⁸ Jonathan Kaplan, FDA data suggest more antibiotics use per pound of meat produced (Oct. 4, 2014), <https://www.nrdc.org/experts/jonathan-kaplan/fda-data-suggest-more-antibiotics-used-pound-meat-produced>.

¹⁹ Although FDA may conclude that additional animal drug uses also pose unacceptable risks and should be discontinued, this petition focuses on growth-promotion and disease-prevention uses. If, as a result of Guidance No. 213, pharmaceutical companies voluntarily remove all growth-promotion indications from product labels by December 31, 2016, we will consider withdrawing our request as it relates to growth-promotion uses.

II. Background

A. FDA's mandatory duty to withdraw approval of drugs not shown to be safe for human health

The Food, Drug, and Cosmetic Act imposes an obligation on FDA to ensure that animal drugs, including animal feed additives, are safe for human health. Antibiotics (and other drugs) cannot be sold for use in livestock without FDA approval.²⁰ FDA cannot approve an animal drug that is not shown to be safe.²¹ And if new information shows that a previously approved drug is no longer shown to be safe, then FDA is required to withdraw approval.²²

A drug used in food animals is safe for humans if there is a "reasonable certainty of no harm to human health" from the use of the drug in animals.²³ In making this assessment, FDA considers only "whether there are human health risks from the use of the drug."²⁴ The agency does not consider any potential benefits, including benefits to human health, from the use of the drug in animals.²⁵

²⁰ 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"); 21 U.S.C. § 360b(a)(1) (providing that "[a] new animal drug shall . . . be deemed unsafe . . . unless" FDA has approved the drug); 21 U.S.C. § 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").

²¹ 21 U.S.C. § 360b(d)(1).

²² 21 U.S.C. § 360b(e)(1)(B) ("The Secretary shall, after due notice and opportunity for hearing to the applicant, issue an order withdrawing approval of an [animal drug] application . . . if the Secretary finds . . . that new evidence . . . shows that such drug is not shown to be safe for use . . ."); 21 C.F.R. § 514.115(b)(3)(ii); *see NRDC v. FDA*, 760 F.3d 151, 172 (2d Cir. 2014) (explaining that if FDA finds, after notice and opportunity for hearing, that an approved animal drug is "not shown to be safe, the statute permits only one remedy – withdrawal of approval").

²³ Guidance No. 209 at 18.

²⁴ FDA, Final Decision of the Commissioner, Withdrawal of Approval of the New Animal Drug Application for Enrofloxacin in Poultry, Docket No. 2000N-1571, at 100 (July 27, 2005).

²⁵ *Id.*

B. The science of antibiotic resistance

Antibiotic²⁶ use creates antibiotic resistance.²⁷ Bacteria spontaneously develop or acquire defenses that prevent certain antibiotics from inhibiting or killing them.²⁸ When populations of bacteria are exposed to antibiotics, susceptible individuals die, while resistant individuals survive and reproduce.²⁹ Over time, the resistant strains of bacteria proliferate.³⁰

Resistance arises in several ways. Spontaneous genetic mutations may confer resistance.³¹ Bacteria also develop resistance by acquiring genetic material – such as small packets of DNA called plasmids – from other bacteria.³² Such genetic transfers may occur between members of different species of bacteria,³³ and non-pathogenic

²⁶ “Antibiotic,” as used in this petition, means “medically important antibiotic,” unless otherwise specified.

Additionally, this petition uses the terms “antibiotic” and “antimicrobial” interchangeably. Technically, “antibiotic” refers specifically to chemicals that kill or inhibit bacteria; antimicrobials include chemicals that kill or inhibit all microorganisms, including fungi, parasites, and viruses. *See* World Health Organization, Antimicrobial Resistance, Fact Sheet No. 194, <http://www.who.int/mediacentre/factsheets/fs194/en/> (last updated April 2015).

²⁷ Centers for Disease Control and Prevention, Antibiotic Resistance Threats in the United States 11 (2013), <http://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf> [hereinafter 2013 CDC report] (“The use of antibiotics is the single most important factor leading to antibiotic resistance around the world.”).

²⁸ National Institute of Allergy and Infectious Diseases, NIAID’s Antibacterial Program: Current Status and Future Directions 2 (2014), <http://www.niaid.nih.gov/topics/antimicrobialresistance/documents/arstrategicplan2014.pdf> [hereinafter 2014 NIAID report].

²⁹ National Library of Medicine, Antibiotic Resistance, <https://medlineplus.gov/antibioticresistance.html>.

³⁰ *Id.*

³¹ 2014 NIAID report at 2.

³² *Id.*

³³ *Id.*; Gebreyes & Thakur, Multidrug-Resistant *Salmonella enterica* Serovar Muenchen from Pigs and Humans and Potential Interserovar Transfer of Antimicrobial Resistance, 49(2) Antimicrobial Agents and Chemotherapy 503, 509 (2005) (noting that “the

bacteria may transfer resistance to pathogenic species.³⁴ A single plasmid may contain genes conferring resistance to multiple classes of antibiotics.³⁵ Because of this, the use of one antibiotic may cause bacteria to develop resistance to several antibiotics.

The health crisis caused by antibiotic resistance grows more pressing every day. The Centers for Disease Control and Prevention (CDC) estimate that antibiotic-resistant bacteria cause at least 2 million illnesses and 23,000 deaths each year,³⁶ and that “[a]bout 1 in 5 resistant infections are caused by germs from food and animals.”³⁷ The latter figure is a rough estimate based on data from just two kinds of bacteria, *Salmonella* and *Campylobacter*.³⁸ Taking other kinds of bacteria or other factors into account could lead to higher estimates.

Emergence of antibiotic-resistant bacteria is now outpacing the ability of medical science to develop new drugs. For example, tetracycline-resistant *Shigella* bacteria were identified in 1959, only nine years after tetracycline was introduced for general medical use; methicillin resistance arose only two years after doctors began to use methicillin; and levofloxacin-resistant pneumococcus – a pathogenic species that can cause

potential transfer of resistance genes between closely related organisms such as *Salmonella* and *E. coli* has been reported previously”).

³⁴ Stecher et al., “Blooming” in the gut: how dysbiosis might contribute to pathogen evolution, 11(4) *Nature Reviews Microbiology* 277 (Apr. 2013).

³⁵ See, e.g., Gebreyes & Thakur, Multidrug-Resistant *Salmonella enterica* Serovar Muenchen from Pigs and Humans and Potential Interserovar Transfer of Antimicrobial Resistance, 49(2) *Antimicrobial Agents and Chemotherapy* 503, 509 (2005) (describing “plasmids carrying multiple antimicrobial resistance genes”).

³⁶ CDC, About Antimicrobial Resistance, <https://www.cdc.gov/drugresistance/about.html> (last updated Sept. 8, 2015).

³⁷ CDC, Antibiotic Resistance from the Farm to the Table, <http://www.cdc.gov/foodsafety/challenges/from-farm-to-table.html> (last updated Nov. 16, 2015).

³⁸ See 2013 CDC report at 15-17.

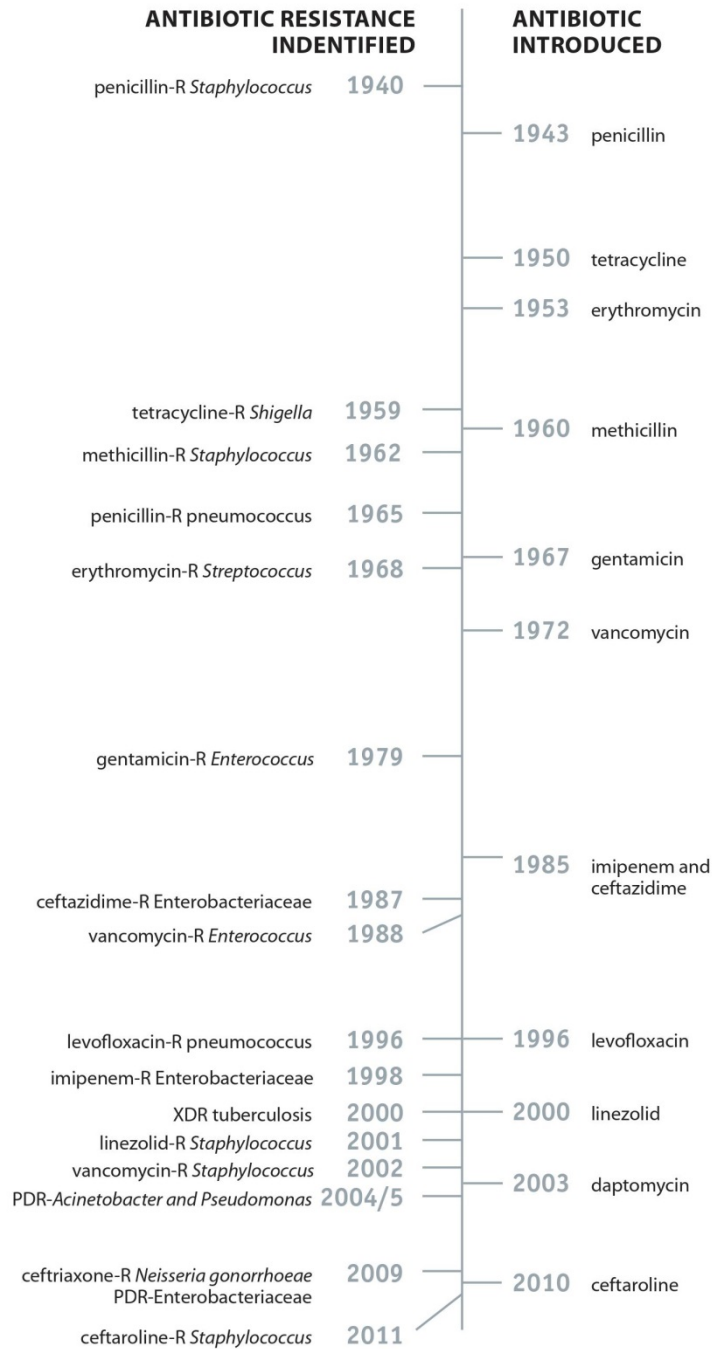
respiratory, sinus, and blood infections³⁹ – was discovered the same year levofloxacin was introduced.⁴⁰ See Figure 1.⁴¹

³⁹ CDC, Pneumococcal Disease, <http://www.cdc.gov/pneumococcal/> (last updated June 10, 2015).

⁴⁰ CDC, About Antimicrobial Resistance, <https://www.cdc.gov/drug-resistance/about.html> (last updated Sept. 8, 2015).

⁴¹ Figure 1 is taken from 2013 CDC report at 14. “Antibiotic Introduced” refers to the year that the antibiotic was administered to the general public. See *id.* Thus, penicillin-resistant *Staphylococcus* was discovered three years before penicillin was marketed to the general public (in 1943), *id.*, but twelve years after penicillin was discovered (in 1928). Markel, The real story behind penicillin, *PBS Newshour* (Sept. 27, 2013), <http://www.pbs.org/newshour/rundown/the-real-story-behind-the-worlds-first-antibiotic/>.

Figure 1: Comparison of dates when antibiotics were first introduced for general human use and dates when antibiotic-resistant bacteria were first observed



C. The use of antibiotics in livestock production

The majority of antibiotics sold in the United States are administered to animals. In 2011, 18.2 million pounds of medically important antibiotics were sold for use in food animals,⁴² while 7.25 million pounds were sold for human use.⁴³ (The FDA reports that sales of medically important antibiotics for livestock increased to nearly 21 million pounds in 2014.⁴⁴) The most current data show that livestock antibiotic use accounts for about 73 percent of all medically important antibiotics sold in the United States.⁴⁵

It is likely that most of the antibiotics given to animals are not administered to treat disease. Instead, most are likely used to promote growth, increase feed efficiency, and prevent disease in otherwise healthy animals.⁴⁶

Although economic considerations are irrelevant to FDA's decision whether to withdraw approval for an unsafe animal drug, it is worth noting that it is neither necessary nor cost-effective to use antibiotics for these purposes. Studies in the

⁴² 2014 use report at 42 (8.26 million kg sold for animal use in 2011).

⁴³ FDA, Drug Use Review 2 (Apr. 5, 2012), <http://www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm319435.pdf> (3.29 million kg of antibiotics sold for human use in 2011).

⁴⁴ 2014 use report at 42 (9.48 million kg sold for animal use in 2014).

⁴⁵ The Pew Charitable Trusts, Record-High Antibiotic Sales for Meat and Poultry Production (July 17, 2013), <http://www.pewtrusts.org/en/multimedia/data-visualizations/2013/recordhigh-antibiotic-sales-for-meat-and-poultry-production>.

⁴⁶ 2014 use report at 30 (96 percent of medically important antibiotics administered to animals are given through food or water); Union of Concerned Scientists, *Hogging It: Estimates of Antimicrobial Abuse in Livestock* 18 (2001) (noting that “[a]ntimicrobials given for nontherapeutic purposes [that is, for disease prevention or growth promotion] are usually given to animals mixed in feed,” while antimicrobials given to treat diseases are typically administered through other methods, such as injection); *see also id.* at xii (estimating that 24.6 million pounds of antimicrobials are administered to livestock annually for nontherapeutic purposes; estimate includes antibiotics that are not important for human medicine); USDA, Antibiotic use in U.S. hog production varies by age and purpose (Nov. 30, 2015), <http://www.ers.usda.gov/data-products/chart-gallery/detail.aspx?chartId=55566> (data suggesting that growth-promotion and disease-prevention uses are widespread in swine); USDA, Economics of Antibiotic Use in U.S. Livestock Production 22 (Nov. 2015), <http://www.ers.usda.gov/media/1950577/err200.pdf> (same).

Netherlands and Denmark have demonstrated that reducing antibiotic use does not harm livestock production. To the contrary, swine production in Denmark has increased since the mid-1990s, when the industry began to discontinue the use of antibiotics in livestock for growth promotion and disease prevention.⁴⁷ In the Netherlands, too, swine industry production and profits have remained stable after a ban on the use of antibiotics for growth-promotion and disease-prevention purposes.⁴⁸ In the United States, more than 40 percent of the broiler chicken industry has already committed to phasing out or has phased out the routine use of antibiotics for disease prevention and growth promotion (based on annual data of ready-to-cook chicken).⁴⁹

D. The link between livestock antibiotic use and antibiotic resistance

Scientific studies have long associated the use of antibiotics in livestock and poultry with an increase in the prevalence of antibiotic resistance.⁵⁰ For example, a study

⁴⁷ Maron et al., Restrictions on antimicrobial use in food animal production: an international regulatory and economic survey, 9 *Global Health* 48 (2013), <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3853314/>.

⁴⁸ Bondt & Kortstee, LEI Wageningen UR, Good Practices: Use of Antibiotics 3-7 (2016), <https://www.government.nl/topics/antibiotic-resistance/documents/reports/2016/01/27/good-practices-use-of-antibiotics>.

⁴⁹ See Perdue, Press Release: Perdue Expands No Antibiotics Ever Poultry into Mainstream Grocery, Foodservice (Feb. 26, 2016), [http://www.perduefarms.com/News_Room/Press_Releases/details.asp?id=1372&title=Perdue%20Expands%20NO%20ANTIBIOTICS%20EVER%99%20Poultry%20into%20Mainstream%20Grocery,%20Food service](http://www.perduefarms.com/News_Room/Press_Releases/details.asp?id=1372&title=Perdue%20Expands%20NO%20ANTIBIOTICS%20EVER%99%20Poultry%20into%20Mainstream%20Grocery,%20Food%20service) (announcing that Perdue raises two-thirds of its chickens without antibiotics); Foster Farms, Statement Regarding Antibiotic Stewardship, <http://www.fosterfarms.com/because-we-care/antibiotic-stewardship/> (stating that the company will not use medically important antibiotics for growth promotion or disease prevention) (last visited Aug. 19, 2016); Tyson, Antibiotic Use, <http://www.tysonfoods.com/Media/Position-Statements/Antibiotic-Use.aspx> (stating that the company has “reduced the use of human antibiotics in our broiler chickens by more than 80 percent since 2011”) (last visited Aug. 19, 2016); Bunge, Pilgrim’s Expects 25% of Its Chicken Will Be Antibiotic-Free by 2019, *Wall Street Journal* (Apr. 20, 2015), <http://www.wsj.com/articles/pilgrims-expects-25-of-its-chicken-will-be-antibiotic-free-by-2019-1429564675>; WATT Poultry USA 17 (Mar. 2016) (listing poultry production numbers for top broiler companies).

⁵⁰ The overwhelming majority of scientific studies on this topic have found a link between the use of antibiotics in livestock and antibiotic resistance in humans. The Review on Antimicrobial Resistance recently reported that, of 139 academic studies,

published in the 1970s showed that the intestinal bacteria of chickens fed tetracycline became almost entirely tetracycline-resistant within one week.⁵¹ Another study in Spain found that in *Campylobacter jejuni* isolated from humans, the prevalence of resistance to fluoroquinolone antibiotics rose rapidly, from less than 10 percent to over 80 percent, in the six years after fluoroquinolone was approved for use in poultry and livestock.⁵² A study in the United States likewise found that fluoroquinolone resistance in human *Campylobacter* samples increased after fluoroquinolones were approved for use in livestock, and that contaminated retail chicken with resistant *Campylobacter* was a likely source.⁵³ In recent years, evidence of the link between livestock antibiotic use and antibiotic resistance has grown even stronger, as discussed in Section III.

Conversely, the prevalence of resistance often falls when the use of antibiotics in livestock is restricted. In the 1970s, Levy et al. found that tetracycline resistance in the intestinal flora of people living on a farm in Massachusetts disappeared six months after the farm discontinued use of animal feed containing tetracycline.⁵⁴ Similarly, a study in Denmark found that the prevalence of resistance to erythromycin, vancomycin, and virginiamycin in samples taken from pigs and broiler chickens fell after the use of those

“only seven (five percent) argued that there was no link between antibiotic consumption in animals and resistance in humans, while 100 (72 percent) found evidence of a link.” Review on Antimicrobial Resistance, Antimicrobials in Agriculture and the Environment: Reducing Unnecessary Use and Waste 10 (Dec. 2015), <http://amr-review.org/sites/default/files/Antimicrobials%20in%20agriculture%20and%20the%20environment%20-%20Reducing%20unnecessary%20use%20and%20waste.pdf>.

⁵¹ Levy et al., Changes in intestinal flora of farm personnel after introduction of a tetracycline-supplemented feed on a farm, 295(11) *New England Journal of Medicine* 583 (1976).

⁵² Nachamkin & Blaser, *Campylobacter* 484-85 (2d ed. 2000).

⁵³ Gupta et al., Antimicrobial Resistance among *Campylobacter* Strains, United States, 1997-2001, 10(6) *Emerging Infectious Diseases*, 1102, 1106-07 (2004).

⁵⁴ Levy et al., Changes in intestinal flora of farm personnel after introduction of a tetracycline-supplemented feed on a farm, 295(11) *New England Journal of Medicine* 583, 587 (1976).

antibiotics in animal feed was discontinued.⁵⁵ But the prevalence of resistance may decline slowly,⁵⁶ and in some cases, resistant bacteria may outcompete susceptible bacteria and remain prevalent after antibiotic use is stopped.⁵⁷

E. The spread of antibiotic-resistant bacteria from livestock to humans

As discussed in more detail in Section III, resistant bacteria from industrial animal facilities can spread to humans who are exposed to meat products or livestock. A 2013 survey of retail meat products conducted by the National Antimicrobial Resistance Monitoring System (NARMS) found that 59-62 percent of *E. coli* samples isolated from ground turkey and 17-32 percent of *E. coli* isolated from chicken were resistant to three or more classes of antibiotics.⁵⁸ Studies have shown that “retail meat is a potential vehicle for transmitting virulent, antibiotic-resistant [bacteria] from food animals to humans.”⁵⁹

⁵⁵ Aarestrup et al., Effect of Abolishment of the Use of Antimicrobial Agents for Growth Promotion on Occurrence of Antimicrobial Resistance in Fecal Enterococci from Food Animals in Denmark, 45(7) *Antimicrobial Agents and Chemotherapy* 2054, 2054 (2001).

⁵⁶ See, e.g., 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(2) *Journal of the American Veterinary Medical Association* 201 (Jan. 15, 2010) (finding that prevalence of resistance to various antibiotics declined slowly after farms phased out use of antibiotics in animal feed).

⁵⁷ See, e.g., Luo et al., Enhanced *in vivo* fitness of fluoroquinolone-resistant *Campylobacter jejuni* in the absence of antibiotic selection pressure, 102(3) *Proceedings of the National Academy of Sciences* 541, 541 (2005) (study demonstrating that fluoroquinolone-resistant *Campylobacter jejuni* outcompeted susceptible bacteria of the same species, even when antibiotics were absent).

⁵⁸ National Antimicrobial Resistance Monitoring System, NARMS Integrated Report: 2012-2013, at 26, <http://www.fda.gov/downloads/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/NationalAntimicrobialResistanceMonitoringSystem/UCM453398.pdf>.

⁵⁹ E.g., Davis et al., Intermingled *Klebsiella pneumoniae* Populations Between Retail Meats and Human Urinary Tract Infections, 61 *Clinical Infectious Diseases* 892 (Sept. 15, 2015) (demonstrating that *K. pneumoniae* isolated from retail meat samples are genetically closely-related to *K. pneumoniae* isolated from human patients); Vieira et al., Association Between Antimicrobial Resistance in *Escherichia coli* Isolates from Food Animals and

Farmworkers may be exposed to antimicrobial-resistant bacteria through contact with animals, and may spread these bacteria to the general population.⁶⁰ Antibiotic-resistant bacteria may also leave industrial farming facilities through air,⁶¹ dust,⁶² animal waste,⁶³ or insects⁶⁴ and rodents⁶⁵ that pass through these facilities. As a result,

Blood Stream Isolates from Humans in Europe: An Ecological Study, 8(12) Foodborne Pathogens and Disease 1295 (Dec. 2011) (finding that “[r]esistance in *E. coli* isolates from food animals . . . was highly correlated with resistance in isolates from humans[, which] supports the hypothesis that a large proportion of resistant *E. coli* isolates causing blood stream infections in people may be derived from food sources.”).

⁶⁰ See, e.g., Price et al., Elevated Risk of Carrying Gentamicin-Resistant *Escherichia coli* among U.S. Poultry Workers, 115(12) Environmental Health Perspectives 1738, 1738 (2007) (poultry workers were 32 times more likely to carry gentamicin-resistant *E. coli*, and significantly more likely to carry multidrug-resistant *E. coli*, than members of the general population); Huijsdens et al., Community-acquired MRSA and pig-farming, 5 Annals of Clinical Microbiology and Antimicrobials 26 (2006) (case study of transfer of MRSA bacteria from pigs to a farmworker and his family); 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).

⁶¹ Brooks et al., Microbial and antibiotic-resistant constituents associated with biological aerosols and poultry litter within a commercial poultry house, 408 Science of the Total Environment 4770 (2010); Gibbs et al., Isolation of antibiotic-resistant bacteria from the air plume downwind of a swine confined or concentrated animal feeding operation, 114 Environmental Health Perspectives 1032 (2006); Zhong et al., REP-PCR tracking of the origin and spread of airborne *Staphylococcus aureus* in and around chicken house, 19 Indoor Air 511 (2009); Rule et al., Food animal transport: A potential source of community exposures to health hazards from industrial farming (CAFOs), 1 Journal of Infection and Public Health 33 (2008); McEachran et al., Antibiotics, Bacteria, and Antibiotic Resistance Genes: Aerial Transport from Cattle Feed Yards via Particulate Matter, 123(4) Environmental Health Perspectives 337 (2015).

⁶² Hamscher et al., Antibiotics in Dust Originating from a Pig-Fattening Farm: A New Source of Health Hazard for Farmers?, 111(13) Environmental Health Perspectives 1590, 1590 (Oct. 2003) (antibiotics found in dust from pig farm).

⁶³ 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(18) Applied Environmental Microbiology 5701 (2013); Wichmann et al., Diverse antibiotic resistance genes in dairy cow manure, 2 mBio 1 (2014); Marti et al., Safely coupling livestock and crop production systems: how rapidly do antibiotic resistance genes dissipate in soil following a commercial application of swine or dairy manure?, 10 Applied and Environmental Microbiology 3258 (2014);

communities near industrial farming facilities have an increased risk of exposure to antibiotic-resistant pathogens.⁶⁶

F. Public health authorities' calls for reductions in livestock antibiotic use

Many public health organizations have recognized the risks posed by the routine use of antibiotics in livestock, and have called for action to reduce this use.

The American Academy of Pediatrics (AAP) published a technical report in June 2015, sounding the alarm once again about the human health risks posed by livestock antibiotic use.⁶⁷ The AAP concluded that “the overuse and misuse of antimicrobial agents in veterinary and human medicine is, in large part, responsible for the

Campagnolo et al., Antimicrobial residues in animal waste and water resources proximal to large-scale swine and poultry feeding operations, 299 *Science of the Total Environment* 89 (2002).

⁶⁴ Nichols, Fly Transmission of *Campylobacter*, 11(3) *Emerging Infectious Diseases* 361 (2005) (collecting evidence that flies are vectors for infectious *Campylobacter*).

⁶⁵ Henzler & Opitz, The Role of Mice in the Epizootiology of *Salmonella enteritidis* Infection on Chicken Layer Farms, 36(3) *Avian Diseases* 625 (1992) (finding that a significant portion of mice on poultry farms carried *Salmonella*).

⁶⁶ See, e.g., Casey et al., Industrial Food Animal Production and Community Health, 2(3) *Current Environmental Health Reports* 259 (2015); 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 Medicine* 1980 (2013); Kelesidis & Chow, Proximity to animal or crop operations may be associated with *de novo* daptomycin-non-susceptible *Enterococcus* infection, 142 *Epidemiological Infections* 221, 221 (2014); 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(2) *Infection Control and Hospital Epidemiology* 190, 190 (2014).

⁶⁷ American Academy of Pediatrics, Nontherapeutic Use of Antimicrobial Agents in Animal Agriculture: Implications for Pediatrics, 136(6) *Pediatrics* e1670 (June 2015), <http://pediatrics.aappublications.org/content/pediatrics/136/6/e1670.full.pdf> [hereinafter AAP report]. The 2015 report reaffirms the conclusions of a report the AAP published in 2004. See American Academy of Pediatrics, Nontherapeutic Use of Antimicrobial Agents in Animal Agriculture: Implications for Pediatrics, 114(3) *Pediatrics* 862 (Sept. 2004), <http://pediatrics.aappublications.org/content/pediatrics/114/3/862.full.pdf>.

emergence of antibiotic resistance.”⁶⁸ The report reviewed recent studies and found that “the addition of low doses of antimicrobial agents to the feed of healthy animals over prolonged periods to promote growth and increase feed efficiency or at a range of doses to prevent disease . . . contribute[s] to resistance and create[s] new health dangers for humans.”⁶⁹ Resistance among food-borne pathogens is particularly dangerous for children: the incidence of food-borne pathogen infections is highest among children younger than five.⁷⁰ The AAP concluded that antibiotics should be used “only to treat and control infectious diseases [in livestock] and not to promote growth or to prevent disease routinely.”⁷¹

As of August 2016, a number of medical and scientific organizations and professionals have signed onto a statement “calling for policy measures that will end routine antibiotic overuse in food animal production.”⁷² The statement endorses, among other principles, the principle that “[a]ntibiotics should only be used for therapeutic purposes when indicated to treat sick animals, and in limited circumstances to control disease outbreaks. Antibiotics should not be used to promote animal growth or for routine disease prevention.”⁷³

In November 2015, the World Health Organization called on the livestock industry to “[e]nsure that antibiotics given to animals . . . are only used to control or treat infectious diseases.”⁷⁴ The Society of Infectious Disease Pharmacists has made a similar recommendation: “Given that the vast majority of antibiotics used worldwide are for nontherapeutic agricultural purposes [that is, for disease prevention and growth promotion] and that the transfer of antibiotic resistance to humans is a well-

⁶⁸ 2015 AAP report at e1670.

⁶⁹ 2015 AAP report at e1670.

⁷⁰ 2015 AAP report at e1673.

⁷¹ 2015 AAP report at e1674.

⁷² Principles for Appropriate Livestock and Poultry Antibiotic Use (Aug. 2016).

⁷³ *Id.*

⁷⁴ World Health Organization, Antibiotic Resistance: What the Agricultural Sector Can Do, <http://www.who.int/mediacentre/events/2015/world-antibiotic-awareness-week/infographics-agriculture.jpg?ua=1>. Note that disease “control” does not include disease prevention.

documented consequence, an increased effort to curb antibiotic use in agriculture is critical to a national and global strategy of combating antibiotic resistance.”⁷⁵

The CDC also acknowledges the risks of administering antibiotics to food animals.⁷⁶

G. FDA’s response to the antibiotic-resistance crisis

FDA has long known that the use of antibiotics in livestock production increases the prevalence of antibiotic resistance in food-borne pathogens and other bacteria. In 1972, an FDA Task Force issued a report describing a link between antibiotic resistance and the use of antibiotics in livestock.⁷⁷ The following year, FDA issued a regulation warning that the agency would propose to withdraw all approvals for disease-prevention and growth-promotion uses of antibiotics 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.⁷⁸ 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.”⁷⁹

⁷⁵ Aitken et al., *Agricultural Applications for Antimicrobials. A Danger to Human Health: An Official Position Statement of the Society of Infectious Disease Pharmacists*, 36(4) *Pharmacotherapy* 422, 431 (2016).

⁷⁶ See 2013 CDC report at 11.

⁷⁷ See *Antibiotic and Sulfonamide Drugs in Animal Feeds*, 37 Fed. Reg. 2444, 2444-45 (Jan. 25, 1972).

⁷⁸ *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 the agency 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. 11,664, 11,664 (Mar. 7, 2016).

⁷⁹ *Penicillin-Containing Premixes*, 42 Fed. Reg. 43,772, 43,772 (Aug. 30, 1977); *Tetracycline (Chlortetracycline and Oxytetracycline)-Containing Premixes*, 42 Fed. Reg. 56,264, 56,288 (Oct. 21, 1977).

Although FDA has never rescinded the scientific findings it made in 1977 that some uses of penicillin and tetracyclines in livestock are not shown to be safe, the agency has not held hearings or withdrawn approval for those drug uses. As recently as 2001 to 2010, FDA reviewed the safety of thirty antibiotic animal-feed additives approved for a mix of growth-promotion and disease-prevention uses, applying the safety criteria the agency adopted in its 1973 regulation.⁸⁰ FDA concluded that twenty-six 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.⁸¹ Yet FDA has not, to date, begun proceedings under the Food, Drug, and Cosmetic Act to withdraw approval for growth-promotion or disease-prevention uses of medically important antibiotics.

Instead of conducting mandatory withdrawal proceedings, FDA has issued two non-binding guidance documents intended to phase out the use of antibiotics in livestock for growth-promotion purposes only.

Guidance for Industry No. 209 encourages livestock and pharmaceutical companies to limit the use of certain "medically important" antibiotics to uses "that are considered necessary for assuring animal health" and to seek veterinary oversight and consultation in the use of antibiotic drugs.⁸² Guidance No. 209 discourages the use of these antibiotics "to promote growth or improve feed efficiency," but condones use for disease prevention, as well as for disease treatment and control.⁸³ "Disease prevention," according to FDA, "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."⁸⁴

⁸⁰ See NRDC, *Playing Chicken with Antibiotics 2* (2014), <https://www.nrdc.org/sites/default/files/antibiotic-feed-fda-documents-IB.pdf>.

⁸¹ *Id.* at 7. FDA's 1973 safety criteria require, among other things, that the drug sponsor submit "studies demonstrating that the antibiotics feed additive does not promote resistance to antibiotics used in human medicine." *Id.* Under FDA's current criteria for approving new animal drugs, FDA evaluates the risk that use of the antibiotic in animal feed will promote the emergence of antibiotic-resistant bacteria; the likelihood that a person will be exposed to such resistant bacteria; and the risk that such an exposure will cause harm to human health. *Id.*

⁸² Guidance No. 209 at 21-22.

⁸³ Guidance No. 209 at 21.

⁸⁴ Guidance No. 209 at 21 n.5.

Guidance for Industry No. 213 sets out a voluntary process for pharmaceutical companies to remove so-called production uses (that is, growth-promotion and feed-efficiency uses) from product labels, and change the use conditions of over-the-counter products to require veterinary oversight (either through a prescription or a veterinary feed directive).⁸⁵ Again, Guidance No. 213 does not direct pharmaceutical manufacturers to remove disease-prevention indications from their products.

Because Guidance No. 213 seeks to end only growth-promotion uses, it fails to address the greatest share of the problem, as argued at length in Section III. Growth-promotion uses account for only 10-15 percent of livestock antibiotic use.⁸⁶ Disease-prevention uses constitute a significant fraction of the remainder.⁸⁷

Moreover, the share of antibiotics used for disease prevention may increase under Guidance No. 213. Growth-promotion and disease-prevention uses are similar: both involve low doses of antibiotics administered to entire herds or flocks over long periods of time. In some cases, the doses approved for growth-promotion purposes for a particular antibiotic are identical to those approved for disease-prevention purposes. Thus, even if growth-promotion uses are phased out in name, they may continue under the banner of disease prevention.

⁸⁵ Guidance No. 213 at 6-7.

⁸⁶ Beth Hoffman, *New FDA "Rules" Not Likely to Reduce Antibiotic Use on Farm*, *Forbes*, Dec. 13, 2013, <http://www.forbes.com/sites/bethhoffman/2013/12/13/new-fda-rules-will-not-reduce-antibiotic-use-on-farm/#3c4946e362dd>; Animal Health Institute, Q&A: Final Guidance 213 and VFD 1, <http://www.ahi.org/wp-content/uploads/2013/12/Final-213-AHI-QA.pdf>. William Flynn, the Deputy Director for Science Policy for FDA's Center for Veterinary Medicine, provided this estimate at a hearing of the Maryland General Assembly on November 2, 2015.

⁸⁷ See 2014 use report at 30 (96 percent of medically important antibiotics given to livestock are administered via food or water); Union of Concerned Scientists, *Hogging It: Estimates of Antimicrobial Abuse in Livestock* 18 (2001) (noting that "[a]ntimicrobials given for nontherapeutic purposes [that is, for disease prevention or growth promotion] are usually given to animals mixed in feed," while antimicrobials administered by other methods, such as injection, are typically given to treat diseases); see also PACCARB, *National Action Plan for Combating Antibiotic-Resistant Bacteria* 20 (2015), https://www.whitehouse.gov/sites/default/files/docs/national_action_plan_for_combating_antibiotic-resistant_bacteria.pdf (noting that "antibiotics in feed or water are typically administered to herds or flocks of food-producing animals").

H. Petitioners' previous lawsuit

In May 2011, NRDC, CSPI, FACT, 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 the agency'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. The groups argued that the petition denial was unlawful because it depended on a rationale—the agency's preference for a voluntary approach—that was divorced from the relevant statutory inquiry: whether the challenged drug uses were “shown to be safe.”⁸⁸

The United States District Court for the Southern District of New York ruled for the citizen groups,⁸⁹ but a divided panel of the Second Circuit Court of Appeals reversed.⁹⁰ The panel disagreed that FDA's 1977 findings triggered the requirement to begin withdrawal proceedings. The panel also held that FDA's response to the petitions was adequate. In so doing, the panel “accept[ed] the FDA's determination that its preferred program of voluntary compliance offers greater prospect for immediate and significant reductions in animal antibiotic use” than mandatory withdrawal proceedings.⁹¹

Unfortunately, as described further below, FDA's voluntary program has not reduced livestock antibiotic use, and will not produce significant use reductions in the future.

⁸⁸ 21 U.S.C. § 360b(e)(1)(B).

⁸⁹ *NRDC v. FDA*, 884 F. Supp. 2d 127 (S.D.N.Y. 2012); *NRDC v. FDA*, 872 F. Supp. 2d 318 (S.D.N.Y. 2012).

⁹⁰ *NRDC v. FDA*, 760 F.3d 151 (2d Cir. 2014).

⁹¹ 760 F.3d at 175.

III. FDA must withdraw approval for growth-promotion and disease-prevention uses of medically important antibiotics in livestock

The scientific evidence compels the conclusion that existing approvals for growth-promotion and disease-prevention uses of medically important antibiotics in livestock production are not shown to be safe and must be withdrawn.⁹² We ask that FDA immediately withdraw approval of these drug uses.

When FDA denied our previous petitions making this request, the Second Circuit Court of Appeals reviewed the petition denials and granted the agency a reprieve, on the basis of the agency's assertions "that its preferred program of voluntary compliance offers greater prospect for *immediate and significant reductions* in animal antibiotic use than the pursuit of a potentially contentious withdrawal hearing."⁹³ Chief Judge Katzmann dissented; rather than granting such a reprieve, he would have required FDA to "squarely address the scientific issue of whether those uses have been shown to be safe, which is the sole issue that the statute makes relevant."⁹⁴

Even assuming the evidence supported the Second Circuit's conclusion in 2014 that it was permissible (that is, not arbitrary and capricious) for FDA to prefer a voluntary program to binding withdrawals, the evidence does not support that conclusion today, for two reasons. First, the scientific evidence that livestock antibiotic use threatens human health continues to increase. Second, FDA's voluntary program has not resulted in "immediate" or "significant" reductions in antibiotic use. To the contrary, the use of antibiotics, including medically important antibiotics, in livestock production has increased. This is no surprise, given that Guidance No. 213 condones disease-prevention uses. And, to date, most drug sponsors still have not complied with FDA's request that they voluntarily withdraw growth-promotion indications by December 2016.⁹⁵

Additionally, a fundamental premise of FDA's denial of the previous petitions – a reading of the Food, Drug, and Cosmetic Act that would require the agency to hold

⁹² 21 U.S.C. § 360b(e)(1)(B).

⁹³ 760 F.3d at 175 (emphasis added).

⁹⁴ *Id.* at 192 (Katzmann, J., dissenting).

⁹⁵ FDA, Fifth Biannual Progress Report on Judicious Use of Antimicrobials in Food-producing Animals (June 30, 2016), <http://www.fda.gov/AnimalVeterinary/NewsEvents/CVMUpdates/ucm509403.htm>.

resource-intensive, formal evidentiary hearings before withdrawing approval of animal drugs⁹⁶ – is mistaken. As explained below, neither the Act nor FDA’s regulations require the agency to hold formal hearings. FDA should exercise its discretion to act expeditiously to withdraw approval for the drug uses specified in this petition, by using informal hearing procedures and other available administrative mechanisms to streamline the withdrawal process.

A. Scientific evidence that livestock antibiotic use threatens human health continues to increase

The scientific evidence demonstrating that the use of antibiotics in livestock production is not shown to be safe has grown even stronger since 2011, when we filed our lawsuit. The following discussion samples the recent literature on the link between the use of antibiotics in livestock production and antibiotic-resistant infections in humans.

1. Exposure to antibiotics can make bacteria more dangerous

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).⁹⁷ Studies have also 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.⁹⁸

⁹⁶ See Lesley Kux, Acting Assistant Comm’r for Policy, FDA, Letter to Sarah Klein, Center for Science in the Public Interest, Original Docket No. 99G-0485/CP, New Docket No. FDA-1999-P-1286, at 3 (Nov. 7, 2011); Lesley Kux, Acting Assistant Comm’r for Policy, FDA, Letter to Andrew Maguire, Env’tl. Defense Fund, Original Docket No. 05P-0139/CP, New Docket No. FDA-2005-P-0007, at 3 (Nov. 7, 2011).

⁹⁷ Looft et al., Bacteria, phages and pigs: the effects of in-feed antibiotics on the microbiome at different gut locations, 8 International Society for Microbial Ecology Journal 1566, 1574 (2014).

⁹⁸ Brewer et al., Effects of subtherapeutic concentrations of antimicrobials on gene acquisition events in *Yersinia*, *Proteus*, *Shigella*, and *Salmonella* recipient organisms in

A review published in 2012 concluded that “there is a link between resistance and virulence” in some *E. coli* bacteria – that is, strains of some bacteria that are resistant to antibiotics are more likely to be pathogenic (disease-causing). In some cases, the authors note, that link is physical, or gene-based: one plasmid carries both the genes that encode resistance and the genes that encode virulence.⁹⁹ Therefore, exposure to an antibiotic in livestock could select for virulence genes as well.

Recent studies have reported that *E. coli* carrying a particular, readily transferred form of resistance to colistin¹⁰⁰—a last-resort antibiotic used to treat infections that are resistant to multiple other drugs—have been found on meat samples in China, where the drug is used extensively in animal feed.¹⁰¹ Indeed, “15% of *E. coli* isolates recovered from retail meat products in Guangzhou, China, carried” the colistin-resistance gene, called *mcr-1*.¹⁰² As of September 2016, scientists from over twenty countries, including countries in South Asia, Africa, and South America, as well as Canada and the United States, have identified *mcr-1* in humans or animals.¹⁰³ Colistin-resistant bacteria, which

isolated ligated intestinal loops of swine, 74(8) *American Journal of Veterinary Research* 1078 (2013).

⁹⁹ Da Silva & Mendonça, Association between antimicrobial resistance and virulence in *Escherichia coli*, 3(1) *Virulence* 18 (2012).

¹⁰⁰ Yao et al., Carbapenem-resistant and colistin-resistant *Escherichia coli* co-producing NDM-9 and MCR-1, 16 *Lancet* 288, 288 (Mar. 2016).

¹⁰¹ Maryn McKenna, Apocalypse Pig: The Last Antibiotic Begins to Fail, *National Geographic*, <http://phenomena.nationalgeographic.com/2015/11/21/mcr-gene-colistin/>.

¹⁰² Yao et al., Carbapenem-resistant and colistin-resistant *Escherichia coli* co-producing NDM-9 and MCR-1, 16 *Lancet* 288, 288 (Mar. 2016).

¹⁰³ Mediavilla et al., Colistin- and Carbapenem-Resistant *Escherichia coli* Harboring *mcr-1* and *bla*_{NDM-5}, Causing a Complicated Urinary Tract Infection in a Patient in the United States, 7(4) *Molecular Biology* e01191-16 (July/Aug. 2016) (documenting isolation of colistin-resistance gene from United States patient without recent travel outside the country); European Centre for Disease Prevention and Control, ECDC rapid risk assessment outlines actions to reduce the spread of the *mcr-1* gene (June 17, 2016), http://ecdc.europa.eu/en/press/news/_layouts/forms/News_DispForm.aspx?ID=1436&List=8db7286c-fe2d-476c-9133-18ff4cb1b568 (featuring maps documenting spread of *mcr-1* gene among humans and among food-producing animals); CDC, Newly Reported Gene, *mcr-1*, Threatens Last-Resort Antibiotics, <http://www.cdc.gov/drug>

are also resistant to other antibiotics, have already been observed in infections in human beings,¹⁰⁴ including here in the United States.¹⁰⁵ Liu et al. posit that colistin-resistant bacteria “originated in animals and subsequently spread to people.”¹⁰⁶

2. Resistant bacteria are transferred from livestock to humans and the environment

Because researchers generally lack access to farms, no study has been capable of tracing the complete pathway that particular antibiotic-resistant bacteria travel from livestock to humans. But studies have produced evidence that resistant bacteria travel along each segment of various pathways.

Several recent studies have confirmed earlier findings that antibiotic-resistant bacteria are transmitted to people exposed to farms or livestock. A 2013 study of farmworkers in North Carolina found that workers at conventional (that is, antibiotic-using) farm facilities were more likely to carry livestock-associated methicillin-resistant *S. aureus* (MRSA) and multidrug-resistant *S. aureus* than workers at antibiotic-free facilities.¹⁰⁷ 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.”¹⁰⁸ A 2014 study of hospital patients in Iowa found that patients who lived

resistance/mrc1.html (last updated Aug. 11, 2016) (noting that *mcr-1* gene has been isolated from humans and pigs in the United States).

¹⁰⁴ Maryn McKenna, *Apocalypse Pig: The Last Antibiotic Begins to Fail*, *National Geographic*, <http://phenomena.nationalgeographic.com/2015/11/21/mcr-gene-colistin/>

¹⁰⁵ McGann et al., *Escherichia coli* Harboring *mcr-1* and *bla*_{CTX-M} on a Novel IncF Plasmid: First Report of *mcr-1* in the United States, 60(7) *Antimicrobial Agents and Chemotherapy* 4420 (July 2016).

¹⁰⁶ Liu et al., *Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study*, 16 *Lancet* 166 (Feb. 2016).

¹⁰⁷ 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(7) *PLOS ONE* 1 (2013).

¹⁰⁸ 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).

within one mile of “large swine facilities” were nearly twice as likely to carry MRSA.¹⁰⁹ And a study in Pennsylvania found a significant association between proximity to farms and to crop fields fertilized with swine manure and the prevalence of skin or soft-tissue MRSA infections.¹¹⁰

Recent studies have also confirmed that resistant bacteria may be transmitted from livestock facilities through the air and soil. A 2013 study detected MRSA in the ambient air outside poultry barns and on the ground downwind from the barns.¹¹¹ Another 2013 study found that farm “[s]oil receiving manure was enriched in antibiotic-resistant bacteria and various antibiotic resistance determinants.”¹¹² And a 2015 study confirmed that airborne particulate matter downwind of livestock feedlots contained livestock-associated bacteria and increased levels of “genes encoding resistance to tetracycline antibiotics.”¹¹³

¹⁰⁹ 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(2) Infection Control and Hospital Epidemiology 190, 190 (2014).

¹¹⁰ 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 Medicine 1980 (2013).

¹¹¹ 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(8) Applied and Environmental Microbiology 2759 (2013); see also 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(2) Journal of Agromedicine 149, 151 (2016) (detecting “airborne MRSA inside [a] swine facility and 215 m[eters] downwind of the swine facility”).

¹¹² 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(18) Applied and Environmental Microbiology 5701, 5701 (2013).

¹¹³ McEachran et al., Antibiotics, Bacteria, and Antibiotic Resistance Genes: Aerial Transport from Cattle Feed Yards via Particulate Matter, 123(4) Environmental Health Perspectives 337, 337 (2015).

3. Genetic studies confirm that resistant bacteria are transmitted between livestock 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 2012 study of *E. coli* bacteria isolated from cattle found resistance genes on plasmids that are “highly similar” to plasmids frequently observed in human *E. coli* samples. This observation provides evidence that plasmids are transferred between cattle and humans.¹¹⁴ Similarly, a genetic study of antibiotic-resistant *E. coli* isolates from humans and chicken meat found that 40 percent 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.”¹¹⁵

Another genetic study found evidence that a particular strain of methicillin-resistant *S. aureus* 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.”¹¹⁶ These findings are consistent with a 2015 study’s observation that several antibiotic-resistant genes found in human *S. aureus* may have originated in animals.¹¹⁷

A 2013 genetic analysis of two Danish patients carrying MRSA bacteria found that the MRSA strain from each patient was very similar to MRSA isolated from animals on each patient’s own farm, even though a comparison of the MRSA found in the two humans showed them to be significantly different from one another. These findings

¹¹⁴ 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 *Journal of Antimicrobial Chemotherapy* 582 (2012).

¹¹⁵ 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(4) *Clinical Infectious Diseases* 478 (2013).

¹¹⁶ Price et al., *Staphylococcus aureus* CC398: Host Adaptation and Emergence of Methicillin Resistance in Livestock, 3(1) *mBio* 1 (2012).

¹¹⁷ 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(8) *Applied and Environmental Microbiology* 2759 (2013).

suggest that the MRSA bacteria were transmitted to the patients from their farm animals.¹¹⁸

4. The use of antibiotics in livestock and the prevalence of resistant bacteria in humans, animals, 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 percent 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.”¹¹⁹

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. A 2013 study of intestinal bacteria samples from people in several European countries and the United States found a significantly higher prevalence of genes conferring resistance to antibiotics that were approved for animal use than genes conferring resistance to other antibiotics.¹²⁰

¹¹⁸ Harrison et al., Whole genome sequencing identifies zoonotic transmission of MRSA isolates with the novel *mecA* homologue *mecC*, 5 EMBO Molecular Medicine 509 (2013).

¹¹⁹ 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 Journal of Antimicrobial Chemotherapy 582 (2012).

¹²⁰ Forslund et al., Country-specific antibiotic use practices impact the human gut resistome, 23 Genome Research 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 Nachamkin & Blaser, *Campylobacter* 484-85 (2d ed. 2000); Gupta et al., Antimicrobial Resistance among *Campylobacter* Strains, United States, 1997-2001, 10(6) Emerging Infectious Diseases 1102, 1106-07 (2004); Levy et al., Changes in intestinal flora of farm personnel after introduction of a tetracycline-supplemented feed on a farm, 295(11) New England Journal of Medicine 583, 587 (1976).

5. Restricting certain antibiotic uses in livestock has reduced the prevalence of resistance

In the United States, bans on the use of ciprofloxacin and ceftriaxone in poultry have caused a decrease in the prevalence of resistance to both of those antibiotics among *Salmonella* bacteria.¹²¹

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. After 2007, when ceftiofur was reintroduced, ceftiofur resistance significantly increased among *E. coli* isolates from retail chicken samples.¹²²

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. In 2009, 10.8 percent of samples were resistant, and in 2011, only 3.9 percent were resistant.¹²³ Denmark also severely restricts the use of fluoroquinolones;¹²⁴ 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

¹²¹ Carmen Cordova, FDA's New Interim NARMS Report: Bugs on Food. Some Good News on Salmonella, but Let's Wait for the Rest of It (May 4, 2016), <https://www.nrdc.org/experts/carmen-cordova/fdas-new-interim-narms-report-bugs-food-some-good-news-salmonella-lets-wait>; FDA, 2014-2015 Retail Meat Interim Report (Apr. 28, 2016), <http://www.fda.gov/downloads/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/NationalAntimicrobialResistanceMonitoringSystem/UCM498134.pdf>.

¹²² Dutil et al., Ceftiofur Resistance in *Salmonella enterica* Serovar Heidelberg from Chicken Meat and Humans, Canada 16(1) Emerging Infectious Diseases 48 (2010).

¹²³ Agersø et al., Voluntary ban on cephalosporin use in Danish pig production has effectively reduced extended-spectrum cephalosporinase-producing *Escherichia coli* in slaughter pigs, 68 Journal of Antimicrobial Chemotherapy 569 (2013).

¹²⁴ DANMAP 2014: Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, food and humans in Denmark 16 (2014), http://www.danmap.org/~media/Projekt%20sites/Danmap/DANMAP%20reports/DANMAP%202014/Danmap_2014.ashx [hereinafter DANMAP 2014].

than *Campylobacter* contracted in Denmark.¹²⁵ 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.¹²⁶ And 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.¹²⁷ The study subjects who did carry fluoroquinolone-resistant bacteria appeared to have acquired the bacteria during overseas travel.¹²⁸

This finding applies to individual farms as well. 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 the farms no longer using antibiotics.¹²⁹

¹²⁵ *Id.*

¹²⁶ Speksnijder et al., Reduction of Veterinary Antimicrobial Use in the Netherlands. The Dutch Success Model, 62 *Zoonoses and Public Health* 79, 79, 84 (2015).

¹²⁷ Collignon et al., Fluoroquinolone Resistance in *Campylobacter* Absent from Isolates, Australia, 9(11) *Emerging Infectious Diseases* 1482, 1482 (Nov. 2003).

¹²⁸ *See id.*

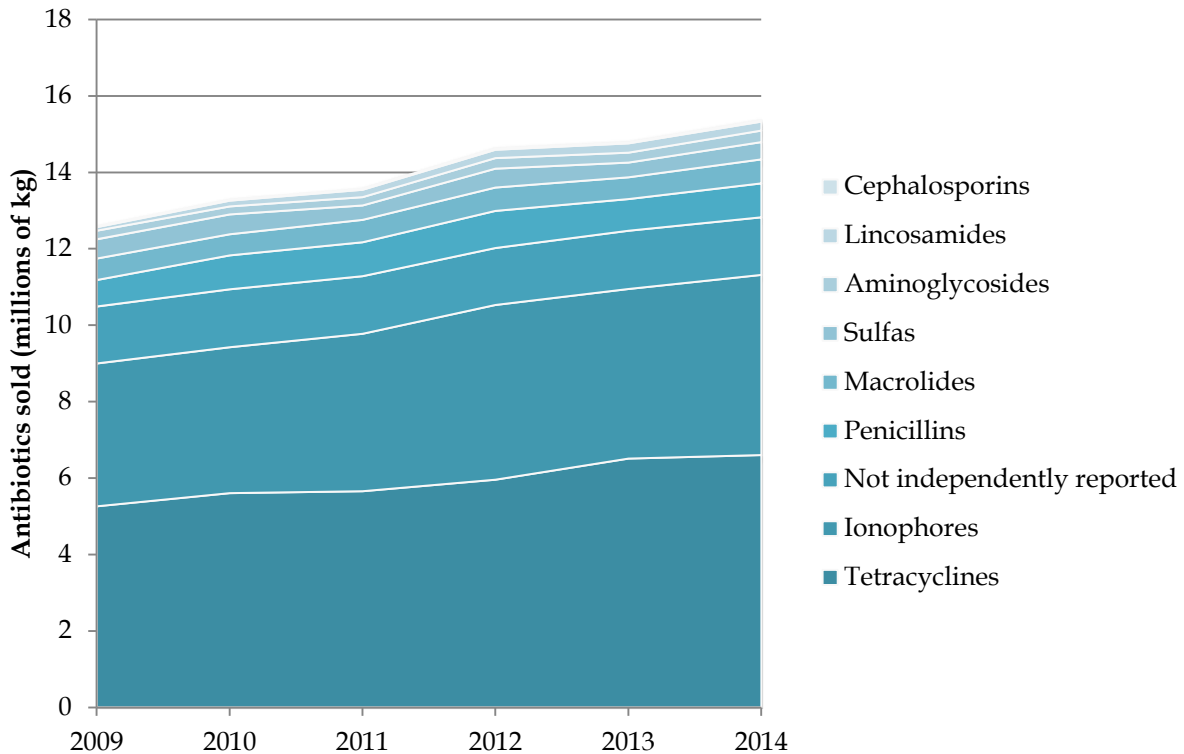
¹²⁹ Sapkota et al., Lower Prevalence of Antibiotic-Resistant Enterococci on U.S. Conventional Poultry Farms that Transitioned to Organic Practices, 119(11) *Environmental Health Perspectives* 1622 (2011).

B. FDA’s voluntary program is not working, and will not work

1. Antibiotic use continues to proliferate

Since FDA launched its voluntary program in 2013, livestock antibiotic use has not decreased but *increased* by nearly 5 percent.¹³⁰ See Figure 2.¹³¹ Between 2013 and 2014 alone, the increase in the total quantity of antibiotics sold for use in animals was 573,165 kilograms.¹³² Sales of every antibiotic for which FDA had individualized data except lincosamides increased between 2013 and 2014; sales of lincosamides decreased 1 percent over that time period, after increasing more than 150 percent between 2009 and 2013.¹³³

Figure 2: Antibiotics sold for use in animals, by type



¹³⁰ 2014 use report at 40.

¹³¹ Figure 2 is based on data from 2014 use report at 40, Table 9.

¹³² *Id.*

¹³³ *Id.*

In 2014, 62 percent of antibiotics sold for use in animals fell into the category FDA considers “medically important” for humans.¹³⁴ (The use of antibiotics that FDA does not consider “medically important” is not necessarily harmless: exposure to one antibiotic may select for resistance to multiple antibiotics, including medically important ones.¹³⁵)

2. FDA’s voluntary program cannot succeed because it allows disease-prevention uses to continue

Guidance No. 213 will not significantly reduce the vast quantities of medically important antibiotics routinely administered to livestock, because it does not restrict the use of these drugs for disease prevention.

FDA condones disease-prevention uses because the agency “considers uses that are associated with the treatment, control, and *prevention* of specific diseases to be therapeutic uses that are necessary for assuring the health of food-producing animals.”¹³⁶ In fact, however, disease-prevention uses are not required for animal health. Livestock producers generally administer antibiotics prophylactically to compensate for the stressful, crowded, and unsanitary conditions that prevail in industrial livestock facilities.¹³⁷ As discussed above, Denmark and the Netherlands have shown that the livestock industry can maintain high rates of meat production without the routine use of medically important antibiotics.¹³⁸ And some studies suggest that

¹³⁴ 2014 use report at 6.

¹³⁵ See, e.g., Looft et al., Bacteria, phages and pigs: the effects of in-feed antibiotics on the microbiome at different gut locations, 8 ISME Journal 1566, 1574 (2014).

¹³⁶ Guidance No. 213 at 4 (emphasis added).

¹³⁷ NRDC Fact Sheet, FDA’s Efforts Fail to End Misuse of Livestock Antibiotics 4 (2015), <https://www.nrdc.org/sites/default/files/fda-guidance-213.pdf>.

¹³⁸ See Aarestrup et al., Changes in the use of antimicrobials and the effects on productivity of swine farms in Denmark, 71(7) American Journal of Veterinary Research 726 (2010); DANMAP 2014 at 30. Antibiotic use in the Dutch livestock industry fell 59 percent between 2009 and 2014. Government of the Netherlands, Antibiotic resistance, <https://www.government.nl/topics/antibiotic-resistance/contents/antibiotic-resistance-in-livestock-farming>. Meat production and industry profits were stable during the same period. Bondt & Kortstee, LEI Wageningen UR, Good Practices: Use of Antibiotics 3-7 (2016), <https://www.government.nl/topics/antibiotic-resistance/documents/reports/2016/01/27/good-practices-use-of-antibiotics>.

good husbandry practices are a more cost-effective means of preventing disease than broad administration of antibiotics.¹³⁹

Because Guidance No. 213 does not forbid disease-prevention uses, FDA's voluntary program will have little, if any, impact on the routine use of medically important antibiotics in livestock production. There are two reasons for this.

First, both FDA and industry officials now acknowledge that antibiotics used solely for growth-promotion purposes account for a relatively small proportion of total livestock antibiotic use. At a hearing of the Maryland General Assembly on November 2, 2015, William Flynn, the Deputy Director for Science Policy of FDA's Center for Veterinary Medicine, estimated that growth-promotion uses account for 10 to 15 percent of overall use. A representative of the Animal Health Institute (AHI), a pharmaceutical industry trade association, has cited the same 10 to 15 percent estimate.¹⁴⁰ Additionally, AHI has stated that "[g]rowth uses of medically important antibiotics represent only a small percentage of overall use, so even if all other factors are static it's unlikely overall use would be greatly affected [by implementation of Guidance No. 213]."¹⁴¹

While only 10 to 15 percent of antibiotic use is for growth promotion, 96 percent of medically important antibiotics given to livestock are administered via feed or water.¹⁴² Available estimates suggest that the bulk of that use is for growth-promotion or disease-prevention purposes.¹⁴³ By failing to eliminate disease-prevention uses, FDA's

¹³⁹ See Berge et al., Targeting therapy to minimize antimicrobial use in preweaned calves: effects on health, growth, and treatment costs, 92(9) J. Dairy Sci. 4707 (2009).

¹⁴⁰ Beth Hoffman, New FDA "Rules" Not Likely to Reduce Antibiotic Use on Farm, *Forbes*, <http://www.forbes.com/sites/bethhoffman/2013/12/13/new-fda-rules-will-not-reduce-antibiotic-use-on-farm/#e24411962dd9> (Dec. 13, 2013).

¹⁴¹ Animal Health Institute, Q&A: Final Guidance 213 and VFD, <http://www.ahi.org/wp-content/uploads/2013/12/Final-213-AHI-QA.pdf> (last visited July 15, 2016).

¹⁴² 2014 use report at 30. This is the percentage of medically important antibiotics that are administered through feed or water; FDA does not provide data concerning what portion of other antibiotics are administered through feed or water. *Id.*

¹⁴³ Union of Concerned Scientists, *Hogging It: Estimates of Antimicrobial Abuse in Livestock* 18 (2001) (noting that "[a]ntimicrobials given for nontherapeutic purposes [that is, for disease prevention or growth promotion] are usually given to animals mixed in feed," while antimicrobials administered by other methods, such as injection, are typically given to treat diseases); see also PACCARB, National Action Plan for

voluntary program could leave in place the lion's share of routine antibiotic use in livestock production.¹⁴⁴

The pharmaceutical industry's acknowledgement that Guidance No. 213 will not significantly reduce overall antibiotic use is supported by examples of ineffective efforts to reduce antibiotic use in other countries. In the Netherlands, for example, total livestock antibiotic use did not decrease following an initial ban on growth-promotion uses alone. But total use did fall by 59 percent after the Netherlands instituted several other measures, including a target for reduction and a ban on disease-prevention uses.¹⁴⁵

Second, FDA's continued approval of disease-prevention indications allows livestock producers to keep using antibiotics at low levels to promote animal growth. When antibiotics are administered for "disease-prevention" purposes, the doses are comparable to those given for growth promotion: low doses to entire herds or flocks for long periods of time.¹⁴⁶ Sometimes the doses approved for growth-promotion purposes for a particular antibiotic are identical to or very similar to those approved for disease-prevention purposes.¹⁴⁷ In these situations, even if the growth-promotion indication is

Combating Antibiotic-Resistant Bacteria 20 (2015), https://www.whitehouse.gov/sites/default/files/docs/national_action_plan_for_combating_antibiotic-resistant_bacteria.pdf (noting that "antibiotics in feed or water are typically administered to herds or flocks of food-producing animals").

¹⁴⁴ FDA's voluntary program contains no specific goals for reducing livestock antibiotic use. By contrast, the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria has set numeric goals for reducing antibiotic use in humans. *See* PACCARB, National Action Plan for Combating Antibiotic-Resistant Bacteria: First 180 Days Report 7 (Nov. 2015), <http://www.hhs.gov/sites/default/files/paccarb-final-report-03312016.pdf>.

¹⁴⁵ Government of the Netherlands, Antibiotic resistance in the livestock industry, <https://www.government.nl/topics/antibiotic-resistance/contents/antibiotic-resistance-in-livestock-farming>; NRDC Fact Sheet, FDA's Efforts Fail to End Misuse of Livestock Antibiotics 5, <https://www.nrdc.org/sites/default/files/fda-guidance-213.pdf>.

¹⁴⁶ *See* NRDC Fact Sheet, FDA's Efforts Fail to End Misuse of Livestock Antibiotics 2, <https://www.nrdc.org/sites/default/files/fda-guidance-213.pdf>.

¹⁴⁷ *See id.*

removed, the same or essentially the same use can continue in the name of disease prevention.

Veterinary oversight is not sufficient to address this problem. Some veterinary organizations (including the American Veterinary Medical Association) have questioned the link between antibiotic use in livestock and the prevalence of antibiotic resistance.¹⁴⁸ Veterinarians who doubt that antibiotic overuse in livestock breeds antibiotic resistance cannot be expected to take steps to reduce antibiotic use.¹⁴⁹

Until FDA takes mandatory action to eliminate not only growth-promotion but also disease-prevention uses of medically important antibiotics, livestock producers can continue to administer these life-saving drugs on a routine basis, promoting the development of antibiotic-resistant bacteria and threatening human health.¹⁵⁰

¹⁴⁸ American Veterinary Medical Association, Antimicrobial Use and Antimicrobial Resistance FAQ, <https://www.avma.org/KB/Resources/FAQs/Pages/Antimicrobial-Use-and-Antimicrobial-Resistance-FAQs.aspx> (last visited July 15, 2016).

¹⁴⁹ Senators Warren, Feinstein, Gillibrand, Blumenthal, Markey, and Booker have called attention to the perils of relying on stakeholders, such as veterinarians, to promote compliance with Guidance No. 213. Letter from Elizabeth Warren, U.S. Senator, to Hon. Robert M. Califf, M.D., Comm'r, FDA 2 (Apr. 12, 2016).

¹⁵⁰ FDA recently announced it was requesting comments to help the agency “develop a process by which sponsors of currently approved, medically important antimicrobial drugs, administered in feed or water to food-producing animals for therapeutic purposes, could establish appropriately targeted durations of use.” See FDA, Establishing Appropriate Durations of Therapeutic Administration, Docket No. FDA-2016-D-2635, at 8 (Sept. 7, 2016) (to be published in the Federal Register on Sept. 14, 2016). FDA noted that “approximately 32% of therapeutic products [defined by FDA to include disease prevention] affected by” Guidance No. 213 currently have “no defined duration of use,” meaning they can be administered indefinitely. See FDA, FDA Seeks Public Input on Next Steps to Help Ensure Judicious Use of Antimicrobials in Animal Agriculture, <http://www.fda.gov/AnimalVeterinary/NewsEvents/CVMUpdates/ucm520110.htm> (Sept. 12, 2016). If FDA were to issue new guidance recommending that drug sponsors voluntarily add defined durations of use to antibiotic products approved for disease-prevention indications, that action would not likely result in significant reductions in livestock antibiotic use, because FDA would still be condoning the routine use of medically important antibiotics for disease prevention, potentially for extended periods of time. Some of the “examples of defined durations of use” that FDA provides in its request for comments could allow weeks of use – e.g., “Feed from weaning up to 120 pounds,” and “Do not feed to chickens over 16 weeks (112 days) of age.” FDA,

3. Pharmaceutical companies have not implemented Guidance No. 213

To date, pharmaceutical companies have done little to implement FDA's voluntary program. FDA predicted in December 2013 that all voluntary label changes pursuant to Guidance No. 213 would be complete within three years.¹⁵¹ But as of September 2016, only 4 of the 293 antibiotic products covered by Guidance 213 had been changed from over-the-counter to prescription dispensing status.¹⁵² Fifty applications had been withdrawn in whole or in part,¹⁵³ but all of them on the ground that the product in question is no longer manufactured or sold.¹⁵⁴ We could identify none that were removed from the market solely in response to Guidance No. 213.

C. FDA should use informal procedures to expedite withdrawal proceedings

Both the Food, Drug, and Cosmetic Act and FDA's own implementing regulations allow the agency to withdraw approval of an animal drug without holding a formal evidentiary hearing.¹⁵⁵ The statute provides that FDA "shall, after due notice and opportunity for hearing to the applicant, issue an order withdrawing approval" of an

Establishing Appropriate Durations of Therapeutic Administration 8. Additionally, the new guidance would not affect approved products that already have defined durations of use, regardless of the length of duration.

¹⁵¹ Guidance No. 213 at 9.

¹⁵² FDA, List of Affected Applications, <http://www.fda.gov/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/JudiciousUseofAntimicrobials/ucm390429.htm> (last updated August 30, 2016).

¹⁵³ *Id.*

¹⁵⁴ See 81 Fed. Reg. 36,790 (June 8, 2016); 81 Fed. Reg. 36,787 (June 8, 2016); 80 Fed. Reg. 76,387 (Dec. 9, 2015); 80 Fed. Reg. 76,384 (Dec. 9, 2015); 80 Fed. Reg. 61,298 (Oct. 13, 2015); 80 Fed. Reg. 61,293 (Oct. 13, 2015); 79 Fed. Reg. 74,021 (Dec. 15, 2014); 79 Fed. Reg. 74,018 (Dec. 15, 2014); 79 Fed. Reg. 37,622 (July 2, 2014); 79 Fed. Reg. 37,621 (July 2, 2014); 79 Fed. Reg. 19,816 (Apr. 10, 2014); 79 Fed. Reg. 19,814 (Apr. 10, 2014); 79 Fed. Reg. 15,441 (Mar. 20, 2014); 79 Fed. Reg. 15,540 (Mar. 20, 2014); 79 Fed. Reg. 10,976 (Feb. 27, 2014); 79 Fed. Reg. 10,974 (Feb. 27, 2014).

¹⁵⁵ See generally Lisa Heinzerling, *Undue Process at the FDA: Antibiotics, Animal Feed, and Agency Intransigence*, 37 Vt. L. Rev. 1007 (2013).

animal drug if the agency finds that new evidence shows that use of the drug is not shown to be safe.¹⁵⁶ 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.¹⁵⁷ Courts have deferred to agencies’ decisions to use informal hearing procedures where a statute requires only an opportunity for “a hearing.”¹⁵⁸

FDA’s implementing regulations likewise allow the agency to use informal hearings to withdraw approval of animal drugs. FDA’s regulations require a formal evidentiary hearing only where the “subject matter of the regulation or order is subject *by statute* to an opportunity for a formal evidentiary public hearing.”¹⁵⁹ 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 regulations also state that the list “imparts no right to a hearing where the *statutory section* provides no

¹⁵⁶ 21 U.S.C. § 360b(e)(1)(B).

¹⁵⁷ 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” (emphasis added)); *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. F.C.C.*, 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”); *City of W. Chicago, Ill. v. Nuclear Regulatory 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).

¹⁵⁸ See *Dominion Energy Brayton Point 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*.”); *Sibley v. U.S. Dep’t of Educ.*, 913 F. Supp. 1181, 1186 n.3 (N.D. Ill. 1995).

¹⁵⁹ 21 C.F.R. § 10.50(a)(1) (emphasis added).

opportunity for a hearing.”¹⁶⁰ As just discussed, the Act does not provide for a formal evidentiary hearing before FDA withdraws approval of an animal drug. Thus, neither do FDA’s regulations impose a formal hearing requirement.

With respect to the action requested here, FDA has concluded that formal evidentiary hearings “would take many years and would impose significant resource demands on the Agency.”¹⁶¹ To avoid any unnecessary delay in protecting the public from unsafe drug uses, FDA should exercise its discretion to use informal hearing procedures to withdraw the drug uses specified in this petition.

Even if FDA concludes that formal hearings are required, however, that should not prevent it from granting this petition. The agency has conducted formal hearings to withdraw approval for other animal drugs that were not shown to be safe,¹⁶² and there is no reason it cannot do so here. FDA’s statutory duty to ensure that animal drugs are safe for human health is paramount, and it cannot avoid that duty simply because upholding it would require time and resources.

Finally, regardless of whether FDA proceeds by formal or informal hearing, Petitioners request that the agency streamline the withdrawal process by taking any or all of the following actions, where appropriate: (a) proceeding by summary adjudication;¹⁶³ (b) combining similar drug products in a single hearing; and (c) conducting a generic rulemaking to establish facts that could be applied in multiple hearings.¹⁶⁴

¹⁶⁰ 21 C.F.R. § 10.50(c) (emphasis added).

¹⁶¹ Letter from Lesley Kux, Acting Assistant Comm’r for Policy, FDA, to Sarah Klein, Center for Science in the Public Interest, Original Docket No. 99G-0485/CP, New Docket No. FDA-1999-P-1286, at 3 (Nov. 7, 2011); Letter from Lesley Kux, Acting Assistant Comm’r for Policy, FDA, to Andrew Maguire, Env’tl. Defense Fund, Original Docket No. 05P-0139/CP, New Docket No. FDA-2005-P-0007, at 3 (Nov. 7, 2011).

¹⁶² *See, e.g.*, FDA, Final Decision of the Commissioner, Withdrawal of Approval of the New Animal Drug Application for Enrofloxacin in Poultry, Docket No. 2000N-1571 (July 27, 2005).

¹⁶³ *See* 21 C.F.R. § 514.200(c)(2).

¹⁶⁴ *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 issues that do not require case-by-case consideration. . . . A contrary holding would require the agency continually to

IV. Conclusion

Every day, more people are infected by dangerous antibiotic-resistant bacteria. These infections are becoming harder to treat, in part because of the prodigious, and increasing, use of medically important antibiotics to promote animal growth and compensate for poor conditions in livestock-production facilities. By failing to take binding action to curtail these drug uses – in spite of the weighty scientific evidence of a mounting threat, the public health community’s urgent calls for action, and the inadequacy of the agency’s own voluntary program – FDA has abdicated its statutory duty to safeguard human health.

FDA must comply with Congress’s command that it withdraw approval for animal drug uses that are not shown to be safe for human health. We request that FDA immediately withdraw approval of both growth-promotion and disease-prevention uses of medically important antibiotics in livestock production.

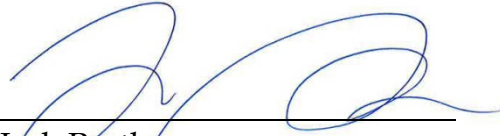
ENVIRONMENTAL IMPACT

FDA’s regulations indicate that withdrawals of drug approvals are 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).

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.

relitigate issues that may be established fairly and efficiently in a single rulemaking proceeding.”).



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APPENDIX

to the Citizen Petition of
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

September 13, 2016

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