**CITIZEN PETITION TO THE FOOD AND DRUG ADMINISTRATION**

Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

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| **CENTER FOR FOOD SAFETY,**<br>660 Pennsylvania Ave, SE, Suite 302<br>Washington, D.C. 20003<br><br>**INSTITUTE FOR AGRICULTURE AND TRADE POLICY,**<br>2105 First Avenue South<br>Minneapolis, MN 55404<br><br>Petitioners,<br><br>***Filed With:***<br><br>**KATHLEEN SEBELIUS,**<br>In her official capacity as,<br>Secretary of the Department of Health and Human Services<br>200 Independence Avenue, S.W.<br>Washington, D.C. 20201<br><br>**MARGARET A. HAMBURG, M.D.**<br>In her official capacity as,<br>Commissioner of the Food and Drug Administration<br><br>**DOCKETS MANAGEMENT BRANCH**<br>Food and Drug Administration<br>Room 1061<br>5630 Fishers Lane<br>Rockville, MD 20852 | Docket Number _____ |

March 14, 2013

***CITIZEN PETITION TO PROHIBIT OR ENJOIN THE USE OF ANTIBIOTICS IN THE PRODUCTION OF DISTILLERS GRAINS SOLD AS ANIMAL FEED FOR FOOD-PRODUCING ANIMALS***

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***CITIZEN PETITION TO PROHIBIT OR ENJOIN THE USE OF ANTIBIOTICS IN THE PRODUCTION OF DISTILLERS GRAINS SOLD AS ANIMAL FEED FOR FOOD-PRODUCING ANIMALS***

## ACTIONS REQUESTED

Pursuant to the right to petition the government clause contained in the First Amendment of the United States Constitution,[1] the Administrative Procedure Act (APA),[2] and the Food and Drug Administration's (FDA) implementing regulations,[3] Petitioners submit this combined citizen petition[4] (the Petition or Citizen Petition) for rulemaking and collateral relief under the authority of 21 U.S.C. § 360b of the Federal Food, Drug, and Cosmetic Act (FFDCA or the Act), the APA 5 U.S.C. § 553(e), and 21 C.F.R. §§ 10.20 and 10.30 to request the Commissioner of FDA to undertake the following actions under the FFDCA pursuant to sections 21 U.S.C. § 342, 5 U.S.C. § 553(e), and 21 C.F.R. § 10.20:

I. Immediately prohibit and enjoin the use of antibiotics in the manufacture of distillers grains with solubles (DGS or distillers grains) sold as animal feed for food-producing animals as adulterated under the FFDCA. Petitioners request that FDA promulgate regulations prohibiting such use. Such regulations shall state that the "use of antibiotics in ethanol production where any distillers grains byproducts may be fed to food-producing animals is hereby prohibited without exception."

II. Or, in the alternative:

A. With respect to FFDCA's new animal drugs provisions, that FDA promulgate regulations to:

i. Immediately deem antibiotics sold by pharmaceutical manufacturers to ethanol producers for DGS production as new animal drugs and

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[1] "Congress shall make no law … abridging … the right of the people … to petition the Government for a redress of grievances." U.S. CONST. amend. I. The right to "petition for a redress of grievances [is] among the most precious of the liberties safeguarded by the Bill of Rights." *United Mine Workers of Am. Dist. 12 v. Ill. State Bar Ass'n*, 389 U.S. 217, 222 (1967). It shares the "preferred place" accorded in our system of government to the First Amendment freedoms, and has "a sanctity and a sanction not permitting dubious intrusions." *Thomas v. Collins*, 323 U.S. 516, 530 (1945). "[A]ny attempt to restrict those [First Amendment] liberties must be justified by clear public interest, threatened not doubtfully or remotely, but by clear and present danger." *Id.* The Supreme Court has recognized that the right to petition is logically implicit in and fundamental to the very idea of a republican form of government. *United States v. Cruikshank*, 92 U.S. 542, 552 (1875).

[2] 5 U.S.C. § 553(e).

[3] 21 C.F.R. §§ 10.20, 10.30.

[4] Petitioners Center for Food Safety and Institute for Agriculture and Trade Policy ("DGS Petitioners") refer to this citizen petition as a "combined" petition because DGS Petitioners' approach to antibiotic residues in distillers grains is two-pronged by seeking prohibition of antibiotics in DGS, alternatively regulation as a new animal drug. *See also infra* Statement of Legal Grounds § I.

therefore require drug sponsors to file new animal drug applications forthwith pursuant to 21 U.S.C. § 360b(a)(1), 21 C.F.R. § 558.3, and 21 C.F.R. § 514.1;

ii. Immediately ban the sale of antibiotics from pharmaceutical manufacturers to ethanol producers for DGS production without approved new animal drug applications.

## PETITIONERS

The **Center for Food Safety** (CFS) is a Washington, D.C. based nonprofit located at 660 Pennsylvania Avenue, S.E., Washington D.C. 20003. Established in 1997, CFS works to protect human health and the environment by curbing the proliferation of harmful food production technologies and by promoting organic and other forms of sustainable agriculture.

The **Institute for Agriculture and Trade Policy** (IATP) is a 501(c)(3) organization located at 2105 First Avenue South, Minneapolis, MN 55404. Established in 1986, IATP works locally and globally at the intersection of policy and practice to ensure fair and sustainable food, farm and trade systems.

## INTRODUCTION

In a boiled-down description, ethanol production is relatively simple. An ethanol producer grinds up a starch-like feedstock such as corn, adds warm water to make a mash, adds yeast, and then waits as the yeast ferments the starch into ethanol and carbon dioxide.[5] The liquid ethanol and carbon dioxide are removed from the fermentation tank and processed as fuel. A byproduct of ethanol fuel production is the leftover mash, or distillers grains (DGS), which ethanol producers typically then sell as animal feed. During ethanol production, however, fermentation tanks routinely become contaminated with bacteria. Yeast is necessary in the fermentation process to convert starch to ethanol, but bacteria can convert those same sugars to lactic or acetic acid. "If the bacteria get out of control, ethanol production yields can drop significantly, an estimated 1 to 5 percent, which is no small economic problem" for ethanol manufacturers.[6] To kill and control bacteria, ethanol producers use antibiotics. These antibiotics are identical, or substantially identical, to antibiotics used in human medicine, including penicillin, virginiamycin, erythromycin, tylosin, or tetracycline.[7] Upon completion of the

[5] *See, e.g.,* JULIA OLMSTEAD, INSTITUTE FOR AGRICULTURE AND TRADE POLICY, FUELING RESISTANCE? ANTIBIOTICS IN ETHANOL PRODUCTION 3 (2009) [hereinafter FUELING RESISTANCE].
[6] FUELING RESISTANCE, *supra* note 5, at 3.
[7] FUELING RESISTANCE, *supra* note 5, at 3.

fermentation process, antibiotics remain in the leftover mash, which is fed to food-producing animals such as poultry, hogs and beef and dairy cattle.

FDA studies, industry-funded studies, and nonprofit organizations' studies all confirm that distillers grains sold as animal feed contain antibiotics. Food-producing animals therefore, in addition to receiving antibiotics as additives to feed or drinking water in an amount approaching 30 million pounds annually,[8] also receive additional non-therapeutic doses of antibiotics through distillers grains. FDA currently does not regulate, monitor, or require reporting of this antibiotic use as required by Section 105 of the annual Animal Drug User Fee Amendments of 2008 (ADUFA) reports.[9] Their use is thus completely at the discretion of the pharmaceutical and ethanol industries. As the sale of DGS can be fully 20% of an ethanol plant's revenue stream,[10] this Petition is not seeking to stop the sale of DGS to animal producers, who rely on DGS for a nutritious and cost-efficient feed; the Petition seeks simply to ensure that the DGS sold to animal producers are free of any antibiotics.

Antibiotic resistance in humans and animals already is a harmful reality, is continuing to increase, and is driven by persistent antibiotic use and overuse. FDA has recognized the problem and committed to address it, and has acknowledged that antibiotic use must be undertaken "judiciously" and eliminated where it is not appropriate or necessary.[11] Antibiotics are not necessary in ethanol production, and their presence in the byproduct fed to animals producing our meat, poultry, dairy and egg products for human consumption is wholly illegal under the FFDCA and the APA.

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[8] Pew Charitable Trusts, *Record-High Antibiotic Sales for Meat and Poultry Production*, Feb. 6, 2013, http://www.pewhealth.org/other-resource/record-high-antibiotic-sales-for-meat-and-poultry-production-85899449119 (stating that livestock farms consumed a record 29.9 million pounds of antibiotics in 2011).

[9] *See* CTR. FOR VETERINARY MED., FDA, 2011 RETAIL MEAT REPORT: NATIONAL ANTIMICROBIAL RESISTANCE MONITORING SYSTEM 6 (2013), *available at* http://www.fda.gov/downloads/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/NationalAntimicrobialResistanceMonitoringSystem/UCM334834.pdf ("The primary purpose of the NARMS retail meat surveillance program is to monitor the prevalence and trends of antimicrobial resistance among foodborne isolates of *Salmonella, Campylobacter, Enterococcus* and *Escherichia coli*.").

[10] FUELING RESISTANCE, *supra* note 5, at 4.

[11] *See, e.g.,* FDA CTR. FOR VETERINARY MED., GUIDANCE FOR INDUSTRY #209: THE JUDICIOUS USE OF MEDICALLY IMPORTANT ANTIMICROBIAL DRUGS IN FOOD-PRODUCING ANIMALS 4 (2012), *available at* http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM216936.pdf ("Antimicrobial resistance, and the resulting failure of antimicrobial therapies in humans, is a mounting public health problem of global significance.") [hereinafter GUIDANCE #209]; FDA, Animal & Veterinary – FDA's Strategy on Antimicrobial Resistance – Questions and Answers, http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm216939.htm (last visited Mar. 12, 2013).

This Citizen Petition submitted by the Petitioners and the undersigned signatories seeks to prohibit and enjoin the inappropriate and unnecessary use of antibiotics in the manufacture of ethanol where the byproduct is consumed by millions of food-producing animals, and requests the promulgation of regulations prohibiting such antibiotic use. Alternatively, should FDA determine it legally cannot or will not prohibit or enjoin such antibiotic use, petitioners request via this citizen petition that FDA regulate the antibiotic use by requiring new animal drug applications.

## STATEMENT OF THE LAW

**Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 301 *et seq.* and relevant regulations:**
*(summarized in pertinent part)*

- The following acts and the causing thereof are prohibited under the FFDCA:[12]

  (a) The introduction or delivery for introduction into interstate commerce of any food, drug, device, tobacco product, or cosmetic that is adulterated or misbranded.

  (b) The adulteration or misbranding of any food, drug, device, tobacco product, or cosmetic in interstate commerce.

  (c) The receipt in interstate commerce of any food, drug, device, tobacco product, or cosmetic that is adulterated or misbranded, and the delivery or proffered delivery thereof for pay or otherwise.

- A food shall be deemed adulterated if:[13]

  (a)(1) If it bears or contains any poisonous or deleterious substance which may render it injurious to health; but in case the substance is not an added substance such food shall not be considered adulterated under this clause if the quantity of such substance in such food does not ordinarily render it injurious to health.

  (a)(2)(A) if it bears or contains any added poisonous or added deleterious substance (other than a substance that is a pesticide chemical residue in or on a raw agricultural commodity or processed food, a food additive, a color additive, or a new animal drug) that is unsafe within the meaning of 21 U.S.C. § 346; or (B) if it bears or contains a pesticide chemical residue that is unsafe within the meaning of 21 U.S.C. § 346a(a); or (C) if it is or if it bears or contains (i) any food additive that is unsafe within the meaning of 21 U.S.C. § 348; or (ii) a new animal drug (or conversion product thereof) that is unsafe within the meaning of 21 U.S.C. § 360b.

[12] 21 U.S.C. § 331.
[13] 21 U.S.C. § 342.

- Under 21 U.S.C. § 360b(a)(1)-(3), new animal drugs, or any feed bearing or containing new animal drugs are deemed unsafe unless a new animal drug application has been approved. Removal of a new animal drug or feed containing a new animal drug shall also be deemed unsafe for such purposes in the event of removal from the establishment of a manufacturer, packer, or distributor of such drug for use in the manufacture of animal feed in any State unless at the time of such removal such manufacturer, packer, or distributor has an unrevoked written statement from the consignee of such drug, or notice from the Secretary, to the effect that, with respect to the use of such drug in animal feed, such consignee (i) holds a license issued under subsection (m) of this section and has in its possession current approved labeling for such drug in animal feed; or (ii) will, if the consignee is not a user of the drug, ship such drug only to a holder of a license issued under subsection (m) of this section.

- An interested person may petition under the FFDCA for the Commissioner to issue, amend, or revoke a regulation or order, or to take or refrain from taking any other form of administrative action.[14]

**Administrative Procedure Act, 5 U.S.C. § 500 *et seq.*** *(summarized in pertinent part)*

- The APA standard applies to FDA decisions under the FFDCA. The applicable standard is whether the agency's decision was arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with the law.[15] As the U.S. Supreme Court has stated:

> Normally, an agency rule would be arbitrary and capricious if the agency has relied on factors which Congress has not intended it to consider, entirely failed to consider an important aspect of the problem, offered an explanation for its decision that runs counter to the evidence before the agency, or is so implausible that it could not be ascribed to a difference in view or the product of agency expertise.[16]

- In general, agency decisions that are "inconsistent with a statutory mandate or that frustrate the congressional policy underlying a statute" are impermissible.[17]

- Under the APA, agencies are required to "give an interested person the right to petition for issuance, amendment, or repeal of a rule."[18]

## SUMMARY OF ARGUMENT

Antibiotics arguably have been the most important class of medicines available to modern man since they were first developed in the 1940s. When used for medical purposes,

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[14] *See* 21 C.F.R. § 10.25.
[15] 5 U.S.C. § 706(2)(A).
[16] *Motor Vehicle Mfrs. Ass'n of U.S., Inc. v. State Farm Mutual Auto. Ins. Co.*, 463 U.S. 29, 43 (1983).
[17] *See Ocean Advocates v. U.S. Army Corps of Eng'rs*, 402 F.3d 846, 858-59 (9th Cir. 2005) (internal citation omitted).
[18] 5 U.S.C. § 553(e).

antibiotics destroy and/or inhibit growth of harmful bacteria, the cause of bacterial infections in humans and animals. In some models of food animal production, antibiotics have found a secondary economic use; they can promote more rapid growth, and the more efficient conversion of feed grains to weight gain (commonly referred to as growth promotion and feed efficiency). Antibiotics for whatever purpose, however, promote the development and spread among bacteria of resistance to one or multiple antibiotics. Over time, antibiotics that might once have been used successfully to treat human or animal disease are no longer effective; substitute treatments often are more expensive, or inherently more toxic or difficult to administer. Also over time, bacteria have evolved clever apparatus for acquiring resistance to multiple antibiotics more quickly. Some bacteria are now resistant to a multitude of antibiotics and are dubbed "superbugs". Because the medical professional faced with a sick individual cannot immediately know to which antibiotics the infection is resistant, the presence of superbugs means that finding a working antibiotic can more difficult, or, ultimately, impossible. The global health implications are unparalleled, with England's Chief Medical Officer calling antimicrobial resistance a "catastrophic threat".[19] To be clear, that threat is sick people being left without viable or efficient treatment options for common ailments. In the U.S., FDA has recognized the importance of antibiotics in the public health sphere. It has committed to "Get Smart" about antibiotics,[20] and undertaken several major initiatives to address what FDA considers "to be a major health threat to the Public Health in the new millennium: the emergence of drug-resistant bacteria."[21]

Under the FFCDA and the APA, FDA has the legal authority and the obligation to address one aspect of this threat; by promulgating regulations to eliminate the use of antibiotics in distillers grain production so that food-producing animals do not consume additional doses of antibiotics. First, antibiotics in DGS production are not necessary or appropriate, and given the public health threats they are contrary to the FFDCA and their use must be stopped. Second, if FDA determines it legally cannot or will not prohibit antibiotics in DGS production, FDA must regulate DGS as new animal drugs. Third, in light of the vast amount of information before

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[19] Sarah Boseley, *New Wave of 'Superbugs' Poses Dire Threat, Says Chief Medical Officer*, THE GUARDIAN, Mar. 10, 2013, *available at* http://www.guardian.co.uk/society/2013/mar/11/superbugs-antibiotics-bacterial-diseases-infections (last visited Mar. 13, 2013).

[20] *See* FDA Consumer Awareness Program, Get Smart: Know When Antibiotics Work, www.cdc.gov/getsmart (last visited Mar. 12, 2013).

[21] *See* FDA, Drugs – Antimicrobial Resistance, http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm135344.htm (last visited Mar. 12, 2013).

FDA regarding antibiotic resistance, and its own recognition of it as a major health problem, failure of FDA to take action requested under this Petition is arbitrary and capricious under the APA. Any other action is contrary to the FFDCA and the APA.

## STATEMENT OF FACTUAL GROUNDS

### I. USE OF DISTILLERS GRAINS AS ANIMAL FEED

Historically, food-producing animals foraged on pasture, or ate hay from alfalfa, clover or other grasses. With the advent of mechanized and industrialized animal farming, however, industrial producers now feed livestock whole or ground corn, soybeans or a combination of feed rations from other grains and oilseeds. Feed is very expensive. For many industrial producers, it accounts for fully 80% of their operation costs. In an effort to decrease costs, industrial producers continually seek cheaper feed alternatives. Increasingly, industrial producers are feeding food-producing animals byproducts from other manufacturing processes. These processes may or may not be related to animal agriculture, crop agriculture, or aquaculture.[22]

In the case of DGS, it is a byproduct of industrial fuel production. The byproduct includes protein, fiber and oil and can be processed even further, in the form of a corn mash and liquid slurry. It is sold as either a wet or dry animal feed called distillers grains with solubles. The solubles "are a nutritious molasses-like liquid created when the some of the slurry water is separated from the mash and condensed."[23] The condensed slurry is then generally added back into distillers grains to boost the nutritional value of the animal feed.[24] Distillers grains with solubles can be sold wet, or heat-dried.[25]

### II. ALL TESTS CONFIRM ANTIBIOTICS ARE PRESENT IN DISTILLERS GRAINS

FDA has announced that it intends to publish "Draft Guidance for Industry – Antibiotic Residues in Distillers Grains Used as Animal Food."[26] The likely foundations for FDA's draft

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[22] Some examples of byproducts are described in FDA, Lesson 6 – Coding Animal Use Products, Industry Code 71 – Byproducts for Animal Foods, http://www.accessdata.fda.gov/scripts/ora/pcb/tutorial/LES6_IND_CODE67_72.htm (last visited Mar. 12, 2013).

[23] JULIA OLMSTEAD, INSTITUTE FOR AGRICULTURE AND TRADE POLICY, BUGS IN THE SYSTEM: HOW THE FDA FAILS TO REGULATE ANTIBIOTICS IN ETHANOL PRODUCTION, 3-4 (2012), *available at* http://www.iatp.org/files/2012_05_02_AntibioticsInEthanol_JO_0.pdf [hereinafter BUGS IN THE SYSTEM].

[24] Id. at 3-4.

[25] Id. at 4 (citing Ohio State University Extension Fact Sheet).

[26] FDA, Animal & Veterinary – Guidances Under Development for 2012 http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm042451.htm (last visited Mar. 12, 2013) (stating the page was last updated Jan. 19, 2012).

voluntary guidance are questionable and more binding action is necessary. FDA has twice–in 2008 and again 2010–found antibiotic residues in DGS, thus to protect human health and the environment, antibiotics in DGS must be banned. Despite this finding FDA has refused to publish the complete 2008 study results and apparently is still pursuing a guidance document. Apparently FDA employees have stated, without explanation, that FDA would "never" release the results.[27]

### A. FDA Testing Confirms Antibiotics Are Present in Distillers Grains.

Both of FDA's two studies to date have found antibiotics in DGS. The (unreleased) 2008 FDA study collected and tested 60 DGS samples for residues of virginiamycin (a streptogramin antibiotic), erythromycin, and tylosin (a tetracycline). Forty-five of the analyzed samples (53%) came back positive for antibiotics.[28] Fifteen samples contained residues of virginiamycin, twelve contained erythromycin, and five contained tylosin.[29] Some residues were detected at levels FDA considered "significant" and included residues exceeding 0.50 parts per million (ppm).[30] This amount is well in excess of allowable tolerances for antibiotics.[31] All three of these antibiotics are medically important to humans: erythromycin is frequently used for human illnesses; tylosin may spur cross-resistance to erythromycin; and virginiamycin has an important human analogue, Synercid, which is used as a streptogramin antibiotic.[32]

In 2010, FDA conducted a second round of testing. This time, FDA made the results public in survey format. FDA's 2010 survey was to provide FDA "with a better idea of the extent and level of antibiotics in distillers products" in relation to antibiotic residues to support policy development.[33] FDA's Feed Contaminants Program requested the collection of sixty samples. FDA collected and analyzed forty-six samples: twenty-eight from domestic sources

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[27] BUGS IN THE SYSTEM, *supra* note 23 at 5.
[28] National Grain and Feed Association, *FDA Sampling Detects Antibiotic Residues in Ethanol Distillers Products*, 61 NGFA NEWSLETTER 1 (2009) *available at* http://grist.files.wordpress.com/2009/05/news1-29-09.pdf (citing research of Daniel G. McChesney, Ph.D., Director, FDA CVM Office of Surveillance and Compliance) [hereinafter MCCHESNEY].
[29] *See* MCCHESNEY, *supra* note 28.
[30] Id.
[31] *See, e.g.*, 21 C.F.R. § 556.230 (erythromycin's highest allowable tolerance for residue in meat is 0.125 ppm); 21 C.F.R. § 556.750 (virginiamycin's highest allowable tolerance for residue in meat is 0.4 ppm); 21 C.F.R. § 556.740 (tylosin's highest allowable tolerance for residue is 0.2 ppm).
[32] FUELING RESISTANCE, *supra* note 5, at 3.
[33] Marla Luther, Ph.D., FDA, Animal & Veterinary – *Report of FY 2010 Nationwide Survey of Distillers Products for Antibiotic Residues*, Apr. 4, 2012, *available at* http://www.fda.gov/AnimalVeterinary/Products/AnimalFoodFeeds/Contaminants/ucm300126.htm (last visited Mar. 12, 2013).

and eighteen from imported sources. This time, FDA tested the forty-six samples for a greater range of antibiotics. Instead of limiting the testing to merely three antibiotics, FDA looked for residues of twelve different antibiotics: ampicillin, penicillin G, chlortetracycline, oxytetracycline, tetracycline, clarithromycin, erythromycin, streptomycin, virginiamycin M1, bacitracin A, chloramphenicol, monensin, and tylosin.[34]

Of the positive samples, erythromycin residues were at 0.58 ppm, penicillin residues at 0.24 ppm, virginiamycin M1 (from Canada) residues were at 0.18 ppm, and domestic-sourced virginiamycin M1 residues were at 0.16ppm and 0.15ppm (higher than some residue tolerances in food under 21 C.F.R. § 556.750).[35] The examination method used by the laboratory had a limit of quantitation (LOQ) level for each antibiotic. When FDA found that antibiotics were present, but not quantifiable (below the LOQ), FDA *a priori* determined the DGS were "no longer considered to contain antibiotics."[36] This determination ignores important science; in fact, several published studies demonstrate that low level exposure to antibiotics is significant, from both a microbiological and a public health perspective. Exposure to low levels of antibiotic residues in the gut spurs bacteria there to exchange genetic material, such as the genes that make them resistant to one or multiple antibiotics.[37] Low level antibiotic exposure also can spur resistance by promoting bacteria to mutate, which besides gene transfer is another major way in which new antibiotic resistance forms.[38] A draft abstract on the DGS study from FDA's Center for Veterinary Medicine in fact indicates that erythromycin residues in the DGS did select for resistance in *Enterococcus* bacteria.[39] Thus antibiotics in distillers grains are contributing to the global public health threat of antibiotic resistance. Antibiotic residues in DGS are not then, as pharmaceutical and ethanol industries claim, "inactivated".[40] FDA's failure to prohibit the use of

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[34] Id.
[35] Bugs in the System, *supra* note 28 at 5.
[36] Luther, *supra* note 33.
[37] Heather Allen, Torey Looft, Darrell Bayles DO et al., *Antibiotics in Feed Induce Prophages in Swine Fecal Microbiomes*, 29 MBIO. (2011), *available at* http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3225969/?tool=pubmed [hereinafter Allen & Looft].
[38] Michael Kohanski, Mark DePristo, & James Collins, *Sublethal Antibiotic Treatment Leads to Multidrug Resistance via Radical-Induced Mutagenesis*, 12 MOLECULAR CELL 311 (2010), *available at* http://www.cell.com/molecular-cell/retrieve/pii/S1097276510000286 [hereinafter Kohanski & DePristo].
[39] Bugs In the System, *supra* note 23 at 5, n. 14 (quoting Karen Blickenstaff, Faiza Benahmed, Sonay Bodeis-Jones, Marla Luther, Linda Benjamin & Mark Rasmussen, *Impact of Low Level Antimicrobial Residues in Distillers Grains*, (Abstract at Poster session of Symposium on Biotechnology for Fuel and Chemicals, New Orleans, LA. May 2, 2012)).
[40] *See, e.g.,* Lora Berg, *Co-Product Antibiotic Levels Nearly Nil*, NAT'L HOG FARMER, Mar. 14, 2012, *available at* http://nationalhogfarmer.com/nutrition/co-product-antibiotic-levels-nearly-nil.

antibiotics in distillers grains is contrary to the health protections of the FFDCA and is arbitrary and capricious under the APA. Petitioner CFS has submitted a Freedom of Information Act (FOIA) request to FDA. Nine months after the fact, CFS is still awaiting responses and explanations to the status of its outstanding FOIA request.[41]

### B. IATP Reports Confirm Antibiotics Are Present in Distillers Grains.

IATP has issued two reports on antibiotics in ethanol production and DGS: "Bugs in the System" in 2012; and "Fueling Resistance? Antibiotics in Ethanol Production" in 2009. IATP's 2009 report examined the use of antibiotics in ethanol production, the lack of government oversight of pharmaceutical manufacturers' sale of antibiotics to ethanol producers, the sale of ethanol production's byproduct as animal feed, and analysis based on the limited information FDA released on its 2008 study. IATP's 2009 report concluded that antibiotic use in ethanol production is unnecessary and compounds the problem of widespread antibiotic overuse, therefore contributing to antibiotic resistance, when antibiotics exit the ethanol plant and enter our food supply in the form of residues in distillers grains fed to food-production animals.[42]

In 2012, IATP re-analyzed FDA's 2008 study and examined FDA's 2010 study results. IATP's 2012 report also evaluated FDA's current thinking on antibiotic residues in distillers grains and its continued utter failure to prohibit or regulate them. IATP's 2012 report concluded that the risks to public health from using antibiotics in ethanol production far outweigh the burden of transition to antibiotic-free ethanol production.[43] As noted by IATP, many major ethanol producers already use effective non-antibiotic alternatives to control fermentation reactions.

IATP's 2012 report made four recommendations, the first being that FDA immediately ban the sale of unapproved antibiotics in ethanol production. IATP also recommended that pharmaceutical manufacturers immediately halt marketing antibiotics to the ethanol industry, the ethanol industry immediately stop using antibiotics, and that federal and state agencies should assist ethanol producers using antibiotics with the transition to antibiotic-free systems.

### C. Residual Amounts of Antibiotics in Distillers Grains Are Not "Inactivated."

Simply the fact that antibiotic residues are present in DGS used as animal feed for food-producing animals should alarm FDA. Several reports have acknowledged that residual drug

[41] CFS FOIA to FDA, FOIA Nos. 2012-4433 and 2012-4207 (submitted Jun. 8, 2012).
[42] Fueling Resistance, *supra* note 5, at 3.
[43] Bugs in the System, *supra* note 23 at 10.

traces and low doses of antibiotics are of concern when it comes to antibiotic resistance.[44] FDA's obligation under the FFDCA is to protect against substances which *may* render a food injurious to health; substances which may render food injurious to health shall be deemed to be adulterated under 21 U.S.C. § 342. Thus, FDA should treat with suspicion any claims that minimize the potential public health impact of ingredients mischaracterized as merely "inactivated", "incidental", or that are only "inert" components of antibiotics which remain in the DGS.[45] The presence of antibiotics in DGS is not an innocuous consequence of the ethanol fermentation process; they add to the total burden of resistance-inducing antibiotics introduced into the farm environment, and into the food supply.

The implication that low levels of antibiotics are "inactivated" does not accord with the science suggesting that lower level antibiotic exposure actually may have greater selection pressure for resistance than do higher levels. Bacterial mutation is a major problem with the overuse and misuse of antibiotics.

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[44] Studies indicate that even low exposure, and/or regular exposure to low levels of antibiotics can over time contribute to the development of antibiotic-resistant bacteria. *See, e.g.*, The 1997 World Health Organization Report "The Medical Impact of Antimicrobial Use in Food Animals" stated that "low-level, long-term exposure to antimicrobials may have greater selective potential than short-term, full-dose therapeutic use." World Health Organization, Emerging and other Communicable Diseases, Surveillance and Control, *The Medical Impact of Antimicrobial Use in Food Animals*, at 5, WHO/EMC/ZOO/97.4 (Oct. 1997) *available at* http://whqlibdoc.who.int/hq/1997/WHO_EMC_ZOO_97.4.pdf; *see also* Allen & Looft, *supra* note 37 and Kohanski & DePristo, *supra* note 38.

[45] As an example of the problems with claims that antibiotics in DGS are "inactivated," researchers at the University of Minnesota conducted a study ("the Minnesota Study"), funded by the Minnesota Corn Research and Promotion Council concluding that antibiotics are present in DGS but that the antibiotics were "inactivated." *See* G.C. Shurson et al., *Are Antibiotics a Concern in Distiller's Co-products?*, (Mar. 21, 2012) *available at* http://www.nutriquest.biz/CMSUploads/Antibiotics%20in%20Distiller%20Co-Products%20-%20Dr.%20Jerry%20Shurson%20%28March%2021,%202012%29.pdf [hereinafter Shurson et al. 2012] (last visited Mar. 12, 2013). Note that the Minnesota Study did not find that there were no antibiotics in distiller's grains – in fact, it found that 100% of the samples contained penicillin residue. *Id.* at 13. The Minnesota researchers preferred to characterize these residues as "inactivated," or destroyed during distillation. *Id.* at 25 -28. Furthermore, while the Minnesota Study reported results stating virginiamycin residue was present in only 1.7% of the samples, a close reading of the text reveals that "[u]sing HPLC method . . . resulted 85.7% of the samples containing virginiamycin residues." *Id.* at 13 (emphasis added). In other words, it appears that the Study as reported residue data derived from a detection method known by researchers to be less sensitive than the alternative HPLC method. The Minnesota Study then attempts to further discount the prevalence of virginiamycin residues by stating that no samples had residue concentrations > 1 ppm. *Id.* at 13. The implication does not accord with the science suggesting that lower level antibiotic exposures actually may have greater selection pressure for resistance than do higher levels. Petitioners further note that the Minnesota Study only examined whether the presence of residual antibiotics *inhibited bacterial growth* in two bacteria and it did not, for example, examine whether low levels of antibiotics promote bacterial mutation, which is an important mechanism by which bacteria develop antibiotic resistance. Note that Minnesota Study team members have also been involved in studies such as: Gerald Shurson *Determination of Potential Human Health Benefits from Diets Containing Corn Distiller's Co-products* (Dec. 11, 2011) (proposing to use "nutritional components" in food and nutraceutical markets and that new markets may be developed for corn co-products), *available at* http://www.mncorn.org/research/distillers-grains/determination-potential-human-health-benefits-diets-containing-corn (last visited Mar. 12, 2013).

## III. FDA RECOGNIZES ANTIBIOTIC RESISTANCE AS A PUBLIC HEALTH THREAT

All of the antibiotics found in DGS are medically important in human medicine. Increased presence of antibiotics in our food-producing animals enable bacteria to develop resistance to these and closely-related drugs. Tylosin, for example, is a macrolide antibiotic similar to erythromycin and tylosin exposure may spur bacteria to develop cross-resistance to erythromycin as well. Virginiamycin is a streptogramin antibiotic that may spur cross-resistance to the important human analogue, Synercid.

When antibiotics are used widely and for long periods of time, the infectious organisms the antibiotics are designed to kill are more likely to have developed resistance to them making the drugs less effective for treating infections.[46] The Centers for Disease Control and Prevention (CDC) has stated that "[i]n some cases, the microorganisms have become so resistant that no available antibiotics are effective against them."[47] Years of use, misuse, and overuse of antibiotics has led to emergence of multidrug-resistant "superbugs". As indicated by CDC's list of current disease causing bacteria exhibiting resistance, this is a major public health threat now– one that promises only to worsen in the future. CDC's list currently includes the following bacteria:[48]

> Acinetobacter, Anthrax, Gonorrhea, Group B Streptococcus, Klebsiella pneumonia, Methicillin-resistant Staphylococcus aureus (MRSA), Neisseria meningitis, Shigella, Streptococcus pneumonia, Typhoid fever, Tuberculosis, Vancomycin-resistant enterococci (VRE), and Vancomycin-intermediate / resistant staphylococcus aureus.

The CDC estimates that nearly two million people in the U.S. alone acquire an infection in the hospital, 90 thousand people die each year from these infections, and that "[m]ore than 70 percent of the bacteria that cause these infections are resistant to at least one of the antibiotics commonly used to treat them."[49] Because of growing antibiotic resistance, physicians are

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[46] CDC, About Antimicrobial Resistance: A Brief Overview, http://www.cdc.gov/drugresistance/about.html (last visited Mar. 12, 2013) [hereinafter About Antimicrobial Resistance].
[47] Id.
[48] CDC, Diseases / Pathogens Associated with Antimicrobial Resistance, http://www.cdc.gov/drugresistance/DiseasesConnectedAR.html (last visited Mar. 12, 2013).
[49] *See* FDA, Drugs – Battle of the Bugs: Fighting Antibiotic Resistance, http://www.fda.gov/drugs/resourcesforyou/consumers/ucm143568.htm (last visited Mar. 12, 2013) (stating website last updated Aug. 17, 2011).

turning to more toxic, less well-characterized drugs to which resistance can also develop.[50] The costs of antibiotic resistance are staggering; one study of 1,400 high-risk patients in Chicago determined that 13.5% of the patients (189 people) had antimicrobial-resistant infections that resulted in total medical and societal costs of more than $13 million.[51] That would equate to a per-person cost of almost $70 thousand. Nationally, the added direct costs of treating resistant infections is estimated at $26 billion more each year than if those infections were antibiotic-susceptible; the indirect costs to patients and families from lost work time and productivity adds an additional tens of billions annually to this figure.[52]

But where do these antibiotic-resistant bacteria originate? Over twelve years ago, the United Nations' World Health Organization recognized that a major source of antibiotic-resistant bacteria was in fact food production:

> Since the discovery of the growth-promoting and disease-fighting capabilities of antibiotics, farmers, fish-farmers and livestock producers have used antimicrobials in everything from apples to aquaculture. Currently, only half of all antibiotics are slated for human consumption. The other 50% are used to treat sick animals, as growth promoters in livestock, and to rid cultivated foodstuffs of various destructive organisms. This ongoing and often low-level dosing for growth and prophylaxis inevitably results in the development of resistance in bacteria in or near livestock, and also heightens fears of new resistant strains "jumping" between species…[53]

Research indicates that the use of antibiotics in food animals may reduce the effectiveness of related antibiotics when used to treat humans.[54]

FDA now reports antibiotic sales data indicating that fully 80% of all antibiotics in the U.S. are sold for use in animal agriculture.[55] Ninety percent of these are not injected for sick

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[50] About Antimicrobial Resistance, *supra* note 46.

[51] *See* Rebecca R. Roberts et al., *Hospital and Societal Costs of Antimicrobial-Resistant Infections in a Chicago Teaching Hospital: Implications for Antibiotic Stewardship*, CLINICAL INFECTIOUS DISEASES, Oct. 15, 2009.

[52] *See, e.g.*, *Antibiotic-Resistant Infections Cost the U.S. Healthcare System in Excess of $20 Billion Annually*, PR NEWSWIRE, (Oct. 19, 2009) *available at* http://www.prnewswire.com/news-releases/antibiotic-resistant-infections-cost-the-us-healthcare-system-in-excess-of-20-billion-annually-64727562.html.

[53] PEW COMMISSION ON INDUSTRIAL FARM ANIMAL PRODUCTION, PUTTING MEAT ON THE TABLE: INDUSTRIAL FARM ANIMAL PRODUCTION IN AMERICA 15 (2009) [hereinafter PEW COMMISSION] (citing WORLD HEALTH ORGANIZATION REPORT ON INFECTIOUS DISEASES 2000, OVERCOMING ANTIMICROBIAL RESISTANCE (2000) *available at* http://www.who.int/infectious-disease-report/2000/index.html (last visited Sept. 14, 2012) [hereinafter WHO REPORT ON INFECTIOUS DISEASES]).

[54] Press Release, U.S. Government Accountability Office, The Agricultural Use of Antibiotics and Its Implications for Human Health 3-5 (Apr. 28, 1999), http://www.gao.gov/products/RCED-99-74 (click on "View Report" to see full 1999 GAO Report on Antibiotics).

animals, but rather are added to feed or water for flocks or herds of animals.[56] This does not even account for antibiotics used by the ethanol industry and consumed by food-producing animals.

A recently compiled bibliography of more than 147 published studies across several strands of evidence indicates the breadth of links between antibiotic use in food animals and worsening antibiotic resistance.[57] Three facts are critical for appreciating this connection: first, most foodborne illnesses are zoonoses (infectious diseases that can be transmitted from vertebrate animals to humans); second, the use of antimicrobials in food animals selects for zoonotic bacteria that can transfer resistance genes to human pathogens; and third, foodborne diseases involving resistant bacteria have been associated with an increase in adverse human health consequences.[58,59]

The presence of antibiotics in food-producing animals promotes the emergence of resistant strains of pathogens and presents a significant risk to human health.[60] As the Pew Commission reported, "[b]ecause bacteria reproduce rapidly, resistance can develop relatively quickly in the presence of antimicrobial agents, and once resistance genes appear in the bacterial gene pool, they can be transferred to related and unrelated bacteria. Therefore, increased exposure to antimicrobials (particularly at low levels) increases the pool of resistant organisms

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[55] FDA, 2009 SUMMARY REPORT ON ANTIMICROBIALS SOLD OR DISTRIBUTED FOR USE IN FOOD-PRODUCING ANIMALS (2009), *available at* http://www.fda.gov/downloads/ForIndustry/UserFees/AnimalDrugUserFeeActADUFA/UCM231851.pdf; *see* Robert S. Lawrence, *The Rise of Antibiotic Resistance: Consequences of FDA's Inaction*, ATLANTIC, Jan. 23, 2012, *available at* http://www.theatlantic.com/health/archive/2012/01/the-rise-of-antibiotic-resistance-consequences-of-fdas-inaction/251754/.

[56] THE HUMANE SOCIETY OF THE UNITED STATES, HUMAN HEALTH IMPLICATIONS OF NON-THERAPEUTIC ANTIBIOTIC USE IN ANIMAL AGRICULTURE 1 (2007), *available at* http://www.diningatpenn.com/penn/env/poultry/poultry--hsus-human-health-report-on-antibiotics.pdf (citing A. Anderson et al., *Public Health Consequences of use of antimicrobial agents in agriculture*, *in* THE RESISTANCE PHENOMENON IN MICROBES AND INFECTIOUS DISEASE VECTORS: IMPLICATIONS FOR HUMAN HEALTH AND STRATEGIES FOR CONTAINMENT: WORKSHOP SUMMARY 231-43 (Stacey L. Knobler, et al. eds., 2003).

[57] *See* Jenny Lee and David Wallinga, *No Time to Lose – Science Supporting Public Health Action to Reduce Antibiotic Overuse in Food Animals*, INST. AGRIC. & TRADE POL'Y, Oct. 26, 2012, *available at* http://www.iatp.org/documents/no-time-to-lose.

[58] *See e.g.*, Amee R. Manges et al., *Food-Borne Origins of Escherichia coli Causing Extraintestinal Infections* CLINICAL INFECTIOUS DISEASES (Sept. 1, 2012); Ellen K. Silbergeld et al., *Industrial Food Animal Production, Antimicrobial Resistance, and Human Health*, ANNU. REV. PUBLIC HEALTH (2008).

[59] Somewhat similarly, with respect to the health consequence of viruses, *see, e.g.*, Tom Philpott, *Swine-flu outbreak could be linked to Smithfield factory farms*, GRIST, Apr. 26, 2009, *available at* http://grist.org/article/2009-04-25-swine-flu-smithfield/.

[60] PEW COMMISSION, *supra* note 53 at 15.

and the risk of antimicrobial-resistant infections."[61]

While in office, pediatrician Joshua M. Sharfstein, M.D., the former FDA Deputy Commissioner, testified that "[t]here is increasing evidence that use of antibiotics contributes to the high burden of resistance in bacteria. To avoid the unnecessary development of resistance under conditions of constant exposure, such as for growth promotion or feed-efficiency antibiotics, the use of antimicrobials should be limited to those situations where human and animal health are protected…Purposes other than for the advancement of animal or human health should not be considered judicious use. Eliminating these uses will not compromise the safety of food. As a result, FDA supports ending the use of antibiotics for growth promotion and feed efficiency in the United States."[62]

## IV. ALTERNATIVES TO ANTIBIOTICS EXIST FOR ETHANOL PRODUCERS

In the case of ethanol production, non-antibiotic options are readily available to serve ethanol producers' needs to control bacteria. Bacteria accumulate in fermenters where the flow of the distillation process slows down, such as along turns in piping, heat exchangers, or valves.[63] The most problematic bacteria are a class known as "lactic acid bacteria" that includes *Lactobacillus*, *Pediococcus*, *Leuconostoc* and *Weissella*. According to IATP's research, "[c]leaning and sanitation can help control bacteria populations, but when cleaning is not enough, ethanol producers often turn to alternatives."[64]

Antibiotics are not the only method to control bacteria in ethanol fermentation tanks. Less risky, more cost-competitive options exist. According to IATP's research, there are two primary commercial alternative antimicrobial products available: stabilized chlorine dioxide, and an enzyme derived from hops.[65] The industry has already begun to recognize non-antibiotic alternatives and an increasing number of ethanol producers have adopted alternative antimicrobial products. Approximately 56% of ethanol producers have already switched from antibiotics to using some form of antibiotic alternative.[66] POET, the world's largest producer,

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[61] Id.
[62] *Hearing on H.R. 1549, Preservation of Antibiotics for Medical Treatment Act, Before the H. Comm. on Rules*, 111th Cong. 9 (2009) (statement of Joshua M. Sharfstein, M.D., Principal Deputy Comm'r, Department of Health and Human Services, FDA), *available at* http://www.gpo.gov/fdsys/pkg/CHRG-111hhrg54484/pdf/CHRG-111hhrg54484.pdf.
[63] FUELING RESISTANCE, *supra* note 5, at 3.
[64] Id.
[65] FUELING RESISTANCE, *supra* note 5, at 5.
[66] *See*, *e.g.*, BUGS IN THE SYSTEM, *supra* note 23 at 9, 11.

produces in excess of 1.6 billion gallons of ethanol and 9 billion pounds of DGS each year.[67] As of August 2011, all twenty-seven of POET's ethanol plants are antibiotic-free.[68] Other smaller producers have also gone antibiotic free.[69] Additional producers may be running trials on alternatives.[70] Clearly alternatives are available, and possible for use by ethanol producers.

## V. ETHANOL INDUSTRY EXPLOSION MEANS INCREASED ANTIBIOTIC USE

Ethanol completely dominates the U.S. biofuels industry and its production continues to explode. In 2011, it comprised fully 98% of U.S. biofuel production.[71] During the five years from 2005 to 2010 ethanol production increased dramatically from 4.5 billion gallons per year to 12.5 billion per year.[72] Correspondingly, the U.S. corn supply has diametrically shifted from approximately 0.5% per quarter going towards ethanol use in 1980 to regularly over 40% per quarter in 2011 and 2012.[73]

Simultaneously, the increase of DGS into the marketplace has skyrocketed. In the ten year period from 2000 to 2010, DGS production increased 1,264 % from 2.5 to 34.1 million metric tons per year.[74] This means food-producing animals are not eating unprecedented amounts of byproducts from the ethanol fuel industry; production of DGS is growing at such a fast clip that DGS are replacing corn and soybeans in the U.S. animal feed market.[75] For example, in 1994 to 1995, the United States Department of Agriculture (USDA) estimates that

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[67] "About POET" in *POET CEO Comments on Proposed RFS Volume* Levels (Jan. 31, 2013) *available at http://www.poet.com/pr/poet-ceo-comments-on-proposed-rfs-volume-levels* (last visited Mar. 13, 2013).

[68] BUGS IN THE SYSTEM, *supra* note 23, at 9-10, n.33 (citing Press Release, POET, POET selling certified antibiotic-free distillers grains (Aug. 30, 2011), *available at* http://www.poet.com/pr/poet-selling-certified-antibiotic-free-distillers-grains. Note also that the Press Release states POET and United Egg Producers conducted a study claiming that adding to layer hen diets "can dramatically reduce ammonia emissions." *Id.* While it might have this important result as to ammonia emissions, it is simultaneously equally as important that remain antibiotic-free. While this may seem a "magic bullet" for air pollution and public health problems of industrial feeding operations, it does not address the fact that animals should not be in facilities that rely more on grain feed than pasture-based feed and foraging, which comes naturally to animals.

[69] See, examples of Central Minnesota Ethanol Co-op and ESE Alcohol, Inc. in FUELING RESISTANCE, *supra* note 5, at 5-6.

[70] FUELING RESISTANCE, *supra* note 5, at 5.

[71] USDA Econ. Res. Serv., "U.S. Bioenergy Statistics," http://www.ers.usda.gov/data-products/us-bioenergy-statistics.aspx (last visited Mar. 13, 2013) [hereinafter BIOENERGY STATISTICS].

[72] BUGS IN THE SYSTEM, *supra* note 23, at 3.

[73] BIOENERGY STATISTICS, *supra* note 71, at Tbl. 5 "Corn supply, disappearance, and share of total corn used for ethanol."

[74] BUGS IN THE SYSTEM, *supra* note 23, at 4, n. 5 (citing LINWOOD HOFFMAN AND ALLEN BAKER, MARKET ISSUES AND PROSPECTS FOR U.S. DISTILLERS' GRAINS SUPPLY, USE, AND PRICE RELATIONSHIPS (2010), *available at* http://www.ers.usda.gov/media/107533/fds10k01_1_.pdf [hereinafter HOFFMAN 2010]).

[75] *See* HOFFMAN 2010, *supra* note 74, at 1 ("Potential domestic and export use of U.S. DDGS exceeds current production and is likely to exceed future production as ethanol production continues to grow.").

approximately 1.8 million metric tons of DGS went to animal feed and "residual" uses.[76] By August 2012, the estimated annual use of DGS for animal feed and residual uses had catapulted to 28.6 million metric tons.[77]

The corn industry actually places the production of DGS higher, having jumped from less than 5,000 metric tons per marketing year in 2000 to approximately 37,500 in 2012 and predicts that it will increase to more than 40,000 metric tons in 2015.[78] As many if not the majority of ethanol producers use antibiotics in unregulated amounts, and have limited avenues to profit from the byproducts of ethanol production, Petitioners believe it is safe to assume that as ethanol production increases, so does food-producing animal consumption of DGS with antibiotic residues.[79]

## VI. FDA'S CURRENT APPROACH DOES NOT PROTECT PUBLIC HEALTH OR THE ENVIRONMENT AND PERMITS PHARMACEUTICAL MANUFACTURERS AND ETHANOL PRODUCERS TO SKIRT THE LAW; A PETITION FOR RULEMAKING IS NECESSARY

### A. FDA's Failure to Regulate Contributes to Antibiotic Resistance.

Currently, antibiotics in DGS fed to food-producing animals are completely unregulated. FDA's failure to regulate means that the sales, sources of sales, and quantity of use are unlimited. Thus, FDA is permitting pharmaceutical manufacturers to sell unlimited amounts of antibiotics to ethanol producers on an over-the-counter basis. Ethanol producers can purchase antibiotics from farm and feed supply stores, or even over the Internet.[80] Antibiotics manufacturers may also be overseas and thus subject to lower standards of safety and production than what is required in the U.S. That said, some countries, such as Canada, make distinctions between DGS used for animal feed that are sourced from industrial fuel production processes versus food grade manufacturing processes such as potable alcohol production.[81] Canada's

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[76] BIOENERGY STATISTICS, *supra* note 71, at Tbl. 8 "Dried Distillers Grain with Solubles: Supply and Disappearance."
[76] Id.
[77] Id.
[78] Shurson et al. 2012, *supra* note 45, at 3.
[79] *See* FUELING RESISTANCE, *supra* note 5, at 4 (summarizing FDA data showing a majority of tested ethanol distillers grains contained antibiotic residues).
[80] FUELING RESISTANCE, *supra* note 5, at 4.
[81] Canadian Food Inspection Agency (CFIA), RG-6 Regulatory Guidance: Ethanol Distillers' Grains for Livestock Feed, at 2.0 & 4.4, http://www.inspection.gc.ca/animals/feeds/regulatory-guidance/rg-6/eng/1329275341920/1329275491608 (noting that these additives are not used in potable alcohol distilling, so are not a concern in their byproduct).

approach is that materials coming into fuel production plants are not food grade and thus inappropriate to introduce in to the food system. [82]

Without any dosage limitations or medical oversight, ethanol producers have full discretion over the quantity and frequency of antibiotic use in manufacturing fuel. FDA does not track antibiotic sales to ethanol producers as it does for use in animals.[83] It is thus nearly impossible to estimate with any accuracy the amount of antibiotics the ethanol industry uses.[84] USDA and the U.S. Census Bureau are aware that there is an overall lack of transparency in the U.S. ethanol industry.[85] What is certain, however, is that ethanol production in the U.S. is skyrocketing. Accordingly, so must be the industry's use of antibiotics, the amount of DGS sold to industrial animal producers, and the amount of antibiotics consumed by food-producing animals.

FDA is supposed to closely monitor and regulate the use of antibiotics in food-producing animals, and to build on existing regulations and agency policy. FDA recently published two guidance documents urging limitations on antibiotic use.[86] FDA is also currently under district court orders (stayed pending appeal) to pursue procedural steps to address public petitions to halt non-therapeutic uses of penicillin, tetracycline, and other medically important antibiotics.[87] None of FDA's regulations however, specifically address the present scenario–where antibiotics used in another manufacturing process are then fed to food-producing animals. Without a bare

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[82] See Cheryl Warren, *Canada Considers New Policy for DDGs*, PROGRESSIVE FARMER, Mar. 28, 2008. *See also* CFIA, *supra* note 81, at 4.2(i) (discussing antimicrobial residues in distillers grains and the duty to monitor these substances to avoid surpassing safe thresholds).

[83] BUGS IN THE SYSTEM, *supra* note 23, at 3, n.3 (citing LINWOOD HOFFMAN AND ALLEN BAKER, ECON. RESEARCH SERVICE, USDA, ESTIMATING THE SUBSTITUTION OF DISTILLERS' GRAINS FOR CORN AND SOYBEAN MEAL IN THE U.S. FEED COMPLEX (Oct. 2011), *available at* http://www.ers.usda.gov/media/236568/fds11i01_2_.pdf); *see also* Animal Drug User Fee Act § 105 Antimicrobial Animal Drug Distribution Reports (ADUFA) (as amended 2008), 21 U.S.C. § 360b(l)(3)(A).

[84] FUELING RESISTANCE, *supra* note 5, at 4.

[85] *See, e.g.,* HOFFMAN 2010, *supra* note 74, at 2 ("[Census] production estimates were considered incomplete by many Government and industry analysts. Other production estimates lack transparency and comparability. So, until the U.S. Census Bureau estimates are more complete and reflect ethanol production data, a transparent estimation method would serve both the Government and the industry, offering estimates for the production and consumption of distillers' grains.").

[86] *See* GUIDANCE #209, *supra* note 11; CTR. FOR VETERINARY MED., FDA, DRAFT GUIDANCE FOR INDUSTRY #213: NEW ANIMAL DRUGS AND NEW ANIMAL DRUG COMBINATION PRODUCTS ADMINISTERED IN OR ON MEDICATED FEED OR DRINKING WATER OF FOOD-PRODUCING ANIMALS (2012), *available at* http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM299624.pdf.

[87] *See*, *Natural Resources Defense Council, Inc. v. U.S. F.D.A.*, No. 1:11-cv-03562-JCF (S.D.N.Y 2012) [hereinafter *NRDC v. FDA*] (District Court case closed Aug. 30, 2012; matter on appeal to the Second Circuit, Case Nos. 12-2106 and 12-3607 and oral arguments were held Feb. 8, 2013). *See* Doc. 70 – Memorandum Opinion and Order (Mar. 22, 2012) and Doc. 103 – Memorandum and Order (Aug. 8, 2012).

minimum of protection for the animals or for the American public from inappropriate antibiotic use, FDA is abstaining from its legal duties under the FFDCA and the APA.

### B. Residue Avoidance Program Tools Are Unfunded.

FDA has set standards for withdrawal times for some antibiotics intentionally administered to some food-producing animals,[88] and set tolerance levels for antibiotic residues in these animals' food products,[89] but FDA has no applicable legally binding standards regarding the presence of residual antibiotics in food consumed by the food-producing animals. Disturbingly, Petitioners believe that most livestock operators are not aware that distillers grains contain antibiotics. Livestock producers have a right to know what they are feeding their animals, and to account for these antibiotics in their feed regimens. This need to know is all the more compounded because U.S. residue testing services are severely compromised.

In the 1980s the USDA Food Safety and Inspection Service founded the "Residue Avoidance Program" (RAP). RAP's goal was to reduce the rate of animal residue violations through education rather than enforcement. As part of the program, several universities began the Food Animal Residue Avoidance Databank whose mission is to prevent or mitigate illegal or harmful residues of drugs, pesticides, biotoxins, and other chemical agents in foods of animal origins.[90] The fiscal year 2013 budget proposes <u>completely eliminating</u> the Food Animal Residue Avoidance Databank.[91] After actual and projected annual funding of one million dollars in 2011 and 2012, the President's budget proposal for Fiscal Year 2013 reduces the Food Animal Residue Avoidance Database's funding to nothing.[92] Thus, without funding, educational tools have lost their value and effect, and vehicles such as citizen petitions are absolutely necessary for the public to push FDA to uphold the applicable laws.

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[88] *See, e.g.*, tylosin, 21 C.F.R. § 522.2640(e)(1)(iii); virginiamycin (no withdrawal period except when used in combination with other drugs), 21 C.F.R. §§ 558.635, 558.265(d)(1), & 558.355(f)(1)(xx); and erythromycin, 21 C.F.R. § 522.820(d)(3)(iii) (withdrawal period for cattle).

[89] *See* 21 C.F.R. § 556.230 (erythromycin's highest allowable tolerance residue is 0.125 ppm in poultry tissues, 0.1 ppm in beef and pork tissues); 21 C.F.R. § 556.750 (virginiamycin's highest allowable tolerance residue is 0.4 ppm in some pork products); 21 C.F.R. § 556.230 (tylosin's highest allowable tolerance residue is 0.2 ppm for animal tissues).

[90] Food Animal Residue Avoidance Databank, http://www.farad.org/about/iabout.asp (last visited Mar. 13, 2013).

[91] OFFICE OF MGMT. & BUDGET, EXEC. OFFICE OF THE PRESIDENT, BUDGET OF THE UNITED STATES GOVERNMENT, FISCAL YEAR 2013 at 84 (2012), *available at* http://www.whitehouse.gov/sites/default/files/omb/budget/fy2013/assets/agr.pdf (Program and Financing Table).

[92] Id. at 84.

## STATEMENT OF LEGAL GROUNDS

FDA has the authority to regulate antibiotics in animal feed for food-producing animals, and it has the legal obligation to prohibit and enjoin such antibiotic use. Alternatively, should FDA determine it will not prohibit such use, it must at a minimum regulate antibiotics in ethanol production by regulating the drugs as new animal drugs. Petitioners have the legal right to request FDA promulgate regulations addressing these issues.

### I. FDA MUST PROMULGATE REGULATIONS PROHIBITING AND ENJOINING ANTIBIOTIC USE IN DISTILLERS GRAINS FOR FOOD-PRODUCING ANIMALS

#### A. FDA Has the Authority to Prohibit Antibiotics in Animal Feed for Food-Producing Animals.

FDA is charged with upholding and enforcing a primary purpose of the FFDCA, to protect consumer health and safety.[93] FDA's statutorily-proscribed mission is to "promote the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely manner" and to protect the public health by ensuring that "foods are safe, wholesome, sanitary and properly labeled."[94] The FFDCA "was not designed primarily for protection of merchants and traders; but was intended to protect the consuming public."[95] The statute requires a precautionary approach to the safety of food, drugs, devices and cosmetics.[96]

The framework of the FFDCA prohibits the adulteration or misbranding of products, or the introduction, delivery, or receipt of adulterated or misbranded products into interstate commerce,[97] and by requiring a premarket review of substances that are not generally recognized as safe.[98] FFDCA's scope is very broad and covers all food, drug, device, tobacco, and cosmetic products implicated for human or animal uses. Animal feeds and drugs are regulated under the FFDCA and companion FDA regulations.[99] FDA has a variety of tools available to it under the FFDCA, including injunctions, seizure, and removal of unapproved drugs from the market.

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[93] 21 U.S.C. § 301 et seq.; *see U.S. v. Lane Labs-USA*, 427 F.3d 219, 227 (3d Cir. 2005).
[94] 21 U.S.C. § 393(b)(1)-(2)(A).
[95] *U.S. v. Two Bags, Poppy Seeds*, 147 F.2d 123, 127 (6th Cir. 1945) (discussing the Pure Food and Drugs Act of 1906, which created the FDA and charged it with this duty).
[96] *See, e.g.*, substances which <u>may</u> render a food injurious to health <u>shall</u> be deemed to be adulterated under 21 U.S.C. § 342.
[97] 21 U.S.C. § 331.
[98] 21 U.S.C. § 348.
[99] 21 U.S.C. § 360b governs new animal drugs and animal feed containing such drugs, and 21 C.F.R. Subchapter E, §§ 500-589, addresses animal drugs, feeds and related products.

Currently the Act does not address antibiotic residues in distillers grains sold as animal feed to food-producing animals, and the product is not banned.

Antibiotics in distillers grains fall within the purview of the FFDCA. DGSs are "food" under the FFDCA, as are the animals themselves who consume DGS, and their food products intended for human consumption may be considered "food" under the FFDCA.[100] "The term 'food' means … articles used for food or drink for man or other animals… [and] articles used for components of any such article."[101] The concept of "food" under the FFDCA is intended to be broadly construed to be consistent with the legislature's intent of reaching all persons responsible for adulteration of food.[102] DGS sold to animal producers are also "animal feed" for purposes of the FFDCA as they are "intended for use for food for animals other than man and which is intended for use as a substantial source of nutrients in the diet of the animal, and is not limited to a mixture intended to be the sole ration of the animal."[103] Additionally, distillers grains with antibiotic residues may, as is discussed further in this Petition, qualify as new animal drugs under the FFDCA. All of these substances are under FDA's authority pursuant to the FFDCA, and to uphold the purposes of the FFDCA, to protect consumer health and safety, FDA should prohibit their use.

### B. Distillers Grains Produced with Antibiotics Are Adulterated Under the FFDCA and Must Be Prohibited.

Food is adulterated, and legally impermissible, if it bears or contains any poisonous or deleterious substance which <u>may</u> render it injurious to health.[104] *See also U.S. v. Lexington Mill & Elevator Co.*, 232 U.S. 399, 410-11, 34 S. Ct. 337 (1914) (if there is any possibility that the food will be injurious it may be condemned). If a substance may be injurious, it <u>shall</u> be deemed adulterated.[105] "Adulteration" does not matter if a substance is naturally-occurring or added as part of a manufacturing process. *See, e.g. U.S. v. An Article of Food Consisting of Cartons of Swordfish*, 395 F. Supp. 1184, 1186 (S.D.N.Y. 1975) (imported swordfish containing mercury is "adulterated"); *Community Nutrition Institute v. Young*, 818 F.2d 943 (D.C. Cir. 1987)

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[100] *U.S. v. Tuente Livestock*, 888 F. Supp. 1416, 1424, 1426 (S.D. Ohio 1995) (Court found live hogs to be "food" in FDA action against middlemen for selling pigs whose edible tissues were tainted with illegal residual levels of sulfamethazine).
[101] 21 U.S.C. § 321(f).
[102] *See Tuente Livestock*, 888 F. Supp. at 1426.
[103] 21 U.S.C. § 321(w).
[104] 21 U.S.C. § 342(a)(1).
[105] 21 U.S.C. § 342 (emphasis added).

(intentional blending of contaminated corn with uncontaminated corn is "adulterated"). Beyond the provisions of 21 U.S.C. § 342(a), food is adulterated once an added poisonous or deleterious substance exceeds any regulated tolerance limit.[106] The setting of regulated or tolerance levels are, however, based upon the unavoidability of the substance concerned.[107] Tolerance levels "do not establish a permissible level of contamination where [the substance's presence] is avoidable."[108] In the case of distillers grains, there exist safer and healthier alternatives in the form of DGS produced so as to not be contaminated with antibiotics.[109] Where the alternative is not used, distillers grains are adulterated under the FFDCA.

None of the exceptions to the FFDCA's adulteration provisions apply here. First, there is an exception for quantities that do not "ordinarily" render it injurious to health.[110] The standard for determining whether a substance "ordinarily" is injurious has varied in case law, with three distinct approaches emerging.[111] Where a substance is not naturally occurring in food, and is in fact added, a stricter approach to whether the substance is 'injurious' is merited.[112] With antibiotics, especially low levels that insidiously build resistance over time, there can be no consumable quantity that does not render them injurious to health. The FFDCA's precautionary approach mandates the agency taking position that the exception cannot apply to DGS as it is clear that antibiotics are injurious to health. Thus, DGS with antibiotic residues are an "adulterated" food under 21 U.S.C. § 342(a)(1) and must be prohibited.

Second, compliance with tolerances, regulatory limits, and action levels does not excuse failure to observe the more general statutory prohibition against adulteration or requirements

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[106] 21 C.F.R. § 509.4.
[107] 21 C.F.R. § 509.7.
[108] 21 C.F.R. § 509.7(a).
[109] *Supra* notes 63-70 and accompanying text; *infra* Statement of Factual Grounds § IV.
[110] 21 U.S.C. § 342(a)(1).
[111] *See U.S. v. 2,116 Boxes of Boned Beef Weighing Approximately 154,121 Pounds*, 516 F. Supp. 321, 329-30 (D. Kan. 1981) naming the three approaches as: "(1) injuriousness *per se* from the presence of a poison in however small an amount, rejected by [*U.S. v. Lexington Mill & E. Co.*, 232 U.S. 399, 34 S. Ct. 337 (1914)]; (2) a reasonable possibility of harm for added deleterious or poisonous substances, defined by *Lexington Mill*; and (3) injurious under ordinary uses and under ordinary conditions for naturally occurring substances."), *aff'd*, 726 F.2d 1481, *cert. denied*, 105 S. Ct. 105, 469 U.S. 825, *r'hg denied*, 105 S. Ct. 557, 469 U.S. 1068.. The District Court in *Boxes of Boned Beef* adopted the second "reasonable possibility of harm" test. *Boxes of Boned Beef*, 516 F. Supp. at 330.
[112] *See, e.g.*, *Certified Color Ind. Com. v. Sec'y of Health, E. & W.*, 236 F.2d 866, 869 (2d Cir. 1957) ("if the complained of ingredient is an added one, then the food is adulterated if the substance *may* render it injurious to health") (emphasis in original); *Young v. Cmty. Nutrition Inst.*, 476 U.S. 974, 976-77, 106 S. Ct. 2360 (1986) (finding 21 U.S.C. § 342 makes it "clear" that "food containing a poisonous or deleterious substance in a quantity that ordinarily renders the food injurious to health is adulterated. If the harmful substance in the food is an added substance, then the food is deemed adulterated, even without direct proof that the food may be injurious to health, if the added substance is "unsafe" under 21 U.S.C. § 346.").

such as adherence to current good manufacturing practices (CGMPs).[113] A food is deemed adulterated where "[a]ny poisonous or deleterious substance added to any food, except where such substance is required in the production thereof and cannot be avoided by any good manufacturing practice shall be deemed unsafe…"[114] Failure to adhere to current good manufacturing practices means that a drug "shall be deemed adulterated",[115] and shall be deemed unsafe.[116] The manufacturer of food must at all times utilize quality control procedures which will reduce contamination to the lowest level currently feasible."[117] If DGS qualify as medicated feed or if ethanol producers need feed mill licenses, CGMPs cannot include using antibiotics, which pose a public health risk, when safer alternatives are available.[118] Antibiotic use in the production of ethanol is not required, and can in fact be avoided because efficient and economical alternatives exist. Thus, the use of antibiotics in ethanol production, and the antibiotics in food-producing animal feed, is entirely avoidable, DGS are adulterated under the FFDCA, and must be prohibited.

Lastly, the regulatory approach to "inactivated", "inactive", "incidental" or "inert" ingredients and the results of FDA's own studies debunk the import of biased conclusions to the contrary.[119] The legal upshot of having ingredients categorized as such (by industry) is not without consequence. Several provisions of the FFDCA demonstrate the Act's predilection towards disclosure of ingredients considered "inactive". First, inactive ingredients must be labeled in some manner; failure to label may violate the FFDCA's misbranding provisions.[120] Second, qualitative or quantitative formulation changes in new animal drugs including inactive ingredients require the submission and approval of a new application to FDA.[121] Third, inactive ingredients in new animal drugs must be made public unless extraordinary circumstances are shown.[122] Efforts to claim that antibiotic residues are inactive or inactivated simply split hairs in

[113] 21 C.F.R. § 509.7(b); 21 U.S.C. § 351(a)(2)(B) (adulteration includes not adhering to current good manufacturing practices).
[114] 21 U.S.C. § 346 (emphases added).
[115] 21 C.F.R. § 225.1(a).
[116] 21 U.S.C. § 360b(a).
[117] 21 C.F.R. § 509.7(b).
[118] *See, e.g.*, 21 C.F.R. § 225.1 (medicated feed), 21 U.S.C. §§ 360b(m) (feed mills), 351(a)(2)(B) (CGMPs must be followed).
[119] *See, e.g.,* Lora Berg, *supra* note 40.
[120] *See, e.g.*, 21 U.S.C. § 360b(c)(2)(A)(viii); *see also Loreto v. Proctor & Gamble Co.,* 737 F. Supp. 2d 909, 919-920, n.5 (S.D. Ohio 2010) (discussing misbranding in both active and inactive ingredient listings).
[121] 21 C.F.R. § 514.8(b)(2)(ii)(A).
[122] 21 C.F.R. § 514.11(e)(5).

an effort to entirely avoid the obvious problem, that DGS contain antibiotic residues. Yet, even if DGS antibiotic residues were "inactivated", the FFDCA still requires regulation. The claims of "inactive" do not debunk the fact that the substance *may* render a food injurious to health, in which case it shall be deemed adulterated. Prohibition of antibiotic in DGS used for food-producing animals is the safest approach and the one most consistent with the FFDCA's purpose.

### C. FDA-Approved Uses of Medically Important Antibiotics Do Not Include The Byproducts of Industrial Fuel Production, Thus DGS Are Impermissible and FDA Must Promulgate Regulations Prohibiting Their Use.

None of FFDCA's provisions addressing antibiotics regulate DGS. The approved new animal drug applications for virginiamycin, tylosin, penicillin, or erythromycin do not address antibiotic residues in animal feed from ethanol production. They address increasing rates of weight gain, improving feed efficiency, and some disease treatment.[123] The Animal Medicinal Drug Use Clarification Act of 1994 regulates veterinarian prescription of extralabel uses of certain approved new animal drugs; it does not regulate antibiotics in DGS.[124]

Similarly, none of FDA's Compliance Policy Guides (CPGs) address antibiotics in DGS. However, existing CPGs support the Petitioners' request that FDA prohibit antibiotics in DGS for food-producing animals, for example: CPG § 682.100 "Use of Drug-Contaminated Products in Animal Feed", states that "[a] product contaminated with a drug, but otherwise suitable for use as an ingredient in a feed, may not be used indiscriminately in a feed" and that FDA would consider the use of penicillin-contaminated nonfat dry milk as an ingredient in a non-medicated feed as a violation of the FFDCA;[125] CPG § 680.500 "Unsafe Contamination of Animal Feed from Drug Carryover" provides that cross-contamination of certain unapproved carcinogenic or toxic drugs during feed manufacturing a violation of good manufacturing practices may occur and feed may be adulterated.[126] Other CPGs are not relevant, such as CPG § 682.200 "The Use of Antibiotic Drug Residue By-Products in Animal Feed []" is not applicable because it

[123] *See, e.g.*, 21 C.F.R. § 558.635(d)(1)-(3) (approved uses for virginiamycin); 21 C.F.R. § 558.625(f)(1)(i)-(vi) (approved uses for tylosin); 21 C.F.R. § 558.460(d)(1) (approved uses for penicillin); and 21 C.F.R. § 558.248(c)(1)-(2) (approved uses for erythromycin thiocyanate).
[124] Pub. L. 103-396, 108 Stat. 4153 (Oct. 22, 1994).
[125] FDA, CPG § 682.100 "Use of Drug Contaminated Products in Animal Feed" *available at* http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm074702.htm
[126] FDA, CPG § 680.500 "Unsafe Contamination of Animal Feed from Drug Carryover," *available at* http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm074699.htm.

addresses antibiotic pre-mix feeds.[127] Thus, FDA's own policy guides favor prohibiting contamination of feed from antibiotics, and FDA should promulgate regulations accordingly.

### D. Due to Problem of Antibiotic Resistance, FDA's Failure to Initiate Rulemaking Prohibiting Antibiotics in Distillers Grains, or to Take Other Action, is Arbitrary, Capricious and Otherwise Unlawful.

As discussed above, FDA has the legal authority under the FFDCA's adulteration provisions, and under the FFDCA more generally, to take action regarding the use of antibiotics in distillers grains used as animal feed. As also discussed above, antibiotic resistance is quickly becoming a major public health threat. In at least two ways, FDA is currently violating the APA: for its failure to deem the substance "adulterated" under the Act; and for its failure to initiate rulemaking procedures prohibiting antibiotics in distillers grains. Failure of FDA to act on either or both of these matters is arbitrary, capricious, and otherwise unlawful.

Deeming antibiotics in DGS adulterated, and/or prohibiting antibiotics in DGS by regulation would be entirely consistent with the FFDCA. Thus, FDA's failure to act to date is arbitrary and capricious under the APA.[128] Agency interpretations that are inconsistent with Congressional intent are entirely unreasonable and not entitled to deference.[129] Numerous examples of FDA's approach towards antibiotics are helpful to demonstrate the agency's interpretation of the FFDCA and antibiotics, and support Petitioners' arguments that FDA's failure to act is contrary to the Act and FDA's accompanying regulations. Some of these examples are described below.

### E. Examples of How Failure to Act Under the FFDCA, or Issue Regulations Prohibiting Antibiotics in Distillers Grains Is Contrary to FDA's Own Interpretations and Applications of Its Authority.

FDA's current approach to not regulate antibiotics in DGS is contrary to at least four of its own interpretive documents. Failure of an agency to adhere to its own guidance or interpretive documents, ignoring its own manuals or guidance documents, or abandoning its own customs and practices, can be analyzed as arbitrary and capricious actions under the APA. *See, e.g., Utahns for Better Transp. v. U.S. Dept. of Transp.*, 305 F.3d 1152, 1165 (10th Cir. 2002) ("Agencies are under an obligation to follow their own regulations, procedures, and precedents,

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[127] FDA, CPG § 680.200 "The Use of Antibiotic Drug Residue By-Products in Animal Feed []", *available at* http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm074718.htm

[128] *See* 5 U.S.C. § 706(2)(A).

[129] *See Chevron U.S.A. v. NRDC*, 467 U.S. 837 (1984) (only reasonable agency interpretations are entitled to judicial deference).

or provide a rational explanation for their departure.")(citations omitted); *Lake Mohave Boat Owners Ass'n v. Nat'l Park Serv.*, 138 F.3d 759, 763 (9th Cir. 1998) *Atchinson v. Wichita Board of Trade*, 412 U.S. 800, 808 (1973) (deviation from guidelines can be reviewed as arbitrary and capricious). Here, where the FFDCA is silent as to express treatment of DGS and antibiotics and animal feed, and so are the agency's regulations, agency interpretations are entitled to considerable deference and weight.[130] In addition to the agency interpretations discussed below, FDA has previously publicly stated it supports a ban of non-therapeutic uses of antibiotics in raising food animals.[131] This would necessarily include antibiotics in distillers grains fed to food-producing animals.

First, Guidance for Industry #72 "GMP's for Medicated Feed Manufacturers Not Required to Register and Be Licensed With FDA" states that for medicated <u>and</u> non-medicated animal feed, "[a] most important responsibility of an animal feed manufacturer is to assure that the feed produced-whether medicated or non-medicated-meets the intended specifications and is not adulterated. All feed mixing operations, regardless of size or drugs used, share this responsibility."[132]

Second, FDA has interpreted its authority over animal feed broadly. The Framework of the FDA Animal Feed Safety System (AFSS) "covers the entire continuum of Agency activities from pre-approval of additives for use in feed, to establishing limits on feed hazards, providing education and training, conducting research, performing inspections, and taking enforcement for ensuring compliance with Agency regulations. Furthermore, the AFSS includes oversight of feed production, including, manufacture, labeling, storage, distribution and use of **all** feed at **all** stages of production, whether at commercial or non-commercial establishments."[133]

Third, FDA's 2012 issuance of Guidance for Industry #209 entitled "The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals" supports regulation of

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[130] *See, e.g.*, *Gladstone Realtors v. Village of Bellwood*, 441 U.S. 91, 107, 99 S. Ct. 1601, 1612 (1979).
[131] *Supra* note 62; *see also* FUELING RESISTANCE, *supra* note 5, at 3, n. 5.
[132] CTR. FOR VETERINARY MED., FDA, GUIDANCE FOR INDUSTRY #72: GMP'S FOR MEDICATED FEED MANUFACTURERS NOT REQUIRED TO REGISTER AND BE LICENSED WITH FDA (May 1998, updated Oct. 21, 2010), *available at* http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052386.pdf
[133] FDA, Animal & Veterinary – Fourth Draft: Framework of the FDA Animal Feed Safety System http://www.fda.gov/AnimalVeterinary/SafetyHealth/AnimalFeedSafetySystemAFSS/ucm196795.htm (last visited Mar. 12, 2013) (bold emphasis original).

antibiotics in DGS.[134] Guidance #209 sets forth important premises regarding misuse and overuse of antibiotics, antibiotic resistance, the loss of effectiveness of antibiotics, and proposes voluntary measures. According to FDA, "judicious use" "means that unnecessary or inappropriate use should be avoided."[135] FDA's proposed voluntary framework consisted of two core principles: first, limiting medically important antimicrobial drugs to uses in food-producing animals that are considered necessary for assuring animal health, and second, limiting such drugs to uses in food-producing animals that include veterinary oversight or consultation.[136] While Guidance #209 focuses on the predominant uses of antibiotics in animal agriculture–therapeutic and non-therapeutic uses-through the new animal drug provisions of the FFDCA, FDA also announced it believed that "it is important to broadly consider how antimicrobial drugs are being used."[137] Antibiotics in distillers grains do not have a non-therapeutic function; in fact, they have no agricultural purpose at all. Their role is only in industrial fuel manufacturing. Antibiotics in animal feed with no purpose must be injudicious. "Limited use" does not include the presence of antibiotics that have no therapeutic purpose. Lastly, distillers grains with antibiotic residues are administered wholly without veterinary oversight. All of these factors make antibiotic residues in distillers grains fed to food-producing animals contrary to FDA's current thinking on antibiotics and the risk-mitigating factors as expressed in Guidance #209 and an earlier FDA Guidance, #152 "Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern."

Contemporaneous with FDA's issuance of Guidance # 209, the agency released the proposed text of the new veterinary feed directive (VFD) regulations.[138] The proposed VFD regulations are designed to help transition certain new animal drug products containing medically important antimicrobials from their current over-the-counter (OTC) status to one requiring veterinary oversight.[139] Antibiotics in distillers grains are, as an example, provided by pharmaceutical manufacturers to ethanol producers on an OTC basis.

Fourth, Guidance #152 is premised on the concept that increasing the exposure of bacterial populations to antimicrobial drugs increases the risk of generating resistance to those

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[134] *See* 77 Fed. Reg. 22247 (Apr. 13, 2012) (announcing the draft text of proposed regulation).
[135] GUIDANCE #209, *supra* note 11, at 3.
[136] Id. at 21-22 (emphasis added)
[137] Id. at 17.
[138] 77 Fed. Reg. 22248 (Apr. 13, 2012) (proposing amending 21 C.F.R. §§ 558.3, 558.6).
[139] *See* 77 Fed. Reg. 22247 (Apr. 13, 2012).

antimicrobial drugs. Risk mitigating factors that are considered include such limitations as restricting use of the drug to use by or on the order of a veterinarian.[140]

Lastly, for comparison purposes, FDA has stated in policy documents that if antibiotics are present in a distiller byproduct that is burned as a fuel or disposed of in a another non-food/non-feed manner, they would be considered pesticides and regulated by the U.S. Environmental Protection Agency under the Federal Insecticide, Fungicide, and Rodenticide Act.[141]

To date, FDA has not adhered to its duty under the FFDCA to deem distillers grains with antibiotic residues "adulterated", nor has it used its authority to promulgate regulations prohibiting antibiotics in ethanol production where the byproducts are fed to food-producing animals. FDA's actions to date are arbitrary and capricious, and unlawful.

## II. ALTERNATIVELY, ANTIBIOTICS IN DISTILLERS GRAINS PRODUCTION MUST BE REGULATED AS NEW ANIMAL DRUGS

Antibiotics administered to food-producing animals are "drugs" and "new animal drugs" under the FFDCA, and if not prohibited, must be regulated under the FFDCA. Antibiotics in ethanol production and fed to food-producing animals are new animal drugs under the FFDCA. In relevant part, a "new animal drug" means "any drug[142] intended[143] for use for animals other

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[140] CTR. FOR VETERINARY MED., FDA, GUIDANCE FOR INDUSTRY #152: EVALUATING THE SAFETY OF ANTIMICROBIAL NEW ANIMAL DRUGS WITH REGARD TO THEIR MICROBIOLOGICAL EFFECTS ON BACTERIA OF HUMAN HEALTH CONCERN (2003) *available at* http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052519.pdf; and GUIDANCE #209, *supra* note 11, at 18.

[141] BUGS IN THE SYSTEM, *supra* note 23, at Fig. 4 (citing CTR. FOR VETERINARY MED., FDA, ANNUAL REPORT FISCAL YEAR 2008 58 (2008), *available at* http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofFoods/CVM/UCM186429.pdf).

[142] Under 21 U.S.C. § 321(g)(1), the term "drug" means:

> (A) articles recognized in the official United States Pharmacopœia, official Homœopathic Pharmacopœia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C). A food or dietary supplement for which a claim, subject to sections 343(r)(1)(B) and 343(r)(3) of this title or sections 343(r)(1)(B) and 343(r)(5)(D) of this title, is made in accordance with the requirements of section 343(r) of this title is not a drug solely because the label or the labeling contains such a claim. A food, dietary ingredient, or dietary supplement for which a truthful and not misleading statement is made in accordance with section 343(r)(6) of this title is not a drug under clause (C) solely because the label or the labeling contains such a statement.

*Id.* Antibiotics are included in this category.

than man, including any drug intended for use in animal feed…"[144] None of the exceptions to new animal drugs apply here. Under the FFDCA, "[a] new animal drug shall, with respect to any particular or intended use of such drug, be deemed unsafe" unless a specified exception is met.[145] Where a drug is "safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof…", or where a drug is "as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions."[146] First, there are no approved uses of medically important antibiotics in distillers grains under the FFDCA or FDA regulations. Second, none of the statutory exceptions apply to antibiotics in distillers grains, thus feeding distillers grains with antibiotics to food-producing animals is contrary to the FFDCA. Under 21 U.S.C. § 321(v)(1), distillers grains as animal feed with antibiotic residue are not generally recognized as safe, nor are there proscribed or recommended or suggested conditions for their use. Under 21 U.S.C. § 321(v)(2), any investigations performed to date do not allow a conclusion that antibiotic residue in distillers grains fed to food-producing animals is safe and effective for use.[147]

Antibiotics in distillers grains should alternatively be regulated as new animal drugs because these drugs are medically important to humans and animals, and FDA must exert greater surveillance over antibiotic use. The new animal drug application process offers protections that control the conditions of use of antibiotics and would prevent against overuse. The antibiotics most frequently used in ethanol production, and which are also identified as residues in distillers grains, are all listed as new animal drugs in FDA's public list of approved animal drugs.[148]

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[143] With respect to the intent requirement, the FFDCA defines what "knowingly" or "knew" means that a person with respect to information: "(1) has actual knowledge of the information, or (2) acts in deliberate ignorance or reckless disregard of the truth or falsity of the information." 33 U.S.C. § 321(bb). A person has requisite intent when they act knowingly. It is public knowledge that antibiotics are used in ethanol manufacturing and the byproducts—certainly pharmaceutical and ethanol manufacturers are well aware of antibiotic use in ethanol production for years. *See, e.g.*, public reports such as Hope Deutscher, *Report: Ethanol industry moving away from antibiotic use*, ETHANOL PRODUCER MAGAZINE, Jul. 8, 2009, *available at* http://www.ethanolproducer.com/articles/5855/report-ethanol-industry-moving-away-from-antibiotic-use; *see also* FUELING RESISTANCE, *supra* note 5, and BUGS IN THE SYSTEM, *supra* note 23.
[144] 21 U.S.C. § 321(v).
[145] 21 U.S.C. § 360b(a)(1).
[146] 21 U.S.C. § 321(v)(1) & (2).
[147] See discussion *supra* note 45 regarding the Minnesota Study.
[148] For example, virginiamycin, erythromycin, penicillin, tetracycline and tylosin are listed in various forms (with various application numbers) as active ingredients in FDA's Green Book. Generic Animal Drug and Patent Restoration Act (Nov. 16, 1988). FDA's list is referred to as the "Green Book", is to be updated monthly, and is available to the public online: FDA, Animal & Veterinary – Green Book On-Line (Jan. 2013),

Increased resistance to these medically important drugs should be regulated by the most stringent methods possible, namely by prohibiting their use, but at a minimum by including veterinary professional oversight. In the case of distillers grains with antibiotic residue, the feed is being distributed entirely without veterinary oversight.

The new animal drug application is one the most important FFDCA measures to protect the public from unsafe products by requiring strict compliance with federally-regulated premarket clearance protocols. Antibiotic residues in DGS are not exempt from this process. Antibiotics used in ethanol production, and which leave drug residues that are in turn fed to food-producing animals, are "new animal drugs" within the meaning of the FFDCA and thus, FDA should alternatively promulgate regulations requiring drug sponsors to adhere to the new animal drug application procedures.

## CONCLUSION

Americans are already suffering from the effects of antibiotic resistance. The overuse of antibiotics and overexposure of bacteria to antibiotics are significant drivers of the resistance problem. Eliminating unnecessary antibiotics voluntarily added to ethanol production when alternatives are readily available is both feasible, as well as a necessary preventative step to help ensure the health of all Americans. Because FDA's current stance on DGS is that they are not prohibited, they do not require a new animal drug application or a food additive petition, nor are they GRAS, FDA must conclude that FFDCA is being violated. For the aforementioned reasons, petitioners respectfully request FDA immediately promulgate regulations to prohibit and enjoin the use of antibiotics in ethanol production where the byproduct of the process, distillers grains with solubles, is sold as animal feed for food-producing animals. Alternatively, if FDA determines that it legally cannot prohibit such use, that it promulgate regulations to oversee antibiotics in DGS production as new animal drugs.

In accordance with FDA regulation 21 C.F.R. Part 10.30(e)(2), FDA must respond to the Petition within 180 days or risk arbitrarily and capriciously violating the regulation.

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http://www.fda.gov/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/UCM042847 (last visited Mar. 12, 2013). *See* 21 C.F.R. §§ 558.635 (virginiamycin), 558.625 (tylosin), 558.460 (penicillin) and 558.248 (erythromycin thiocyanate).

## ENVIRONMENTAL IMPACT STATEMENT

The specific actions requested by Petitioners will not cause the release of any substance into the environment. They are categorically excluded from the requirement of environmental documentation under 21 C.F.R. § 25.33(g).

## ECONOMIC IMPACT STATEMENT

The requested information is only required when requested by the Commissioner following the review of the Petition, and therefore an economic impact statement is not provided at this time.

## 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 Petitioners that are unfavorable to the Petition.

In accordance with the APA, Petitioners request that FDA provide an answer to this Petition within a reasonable time.[149]

Respectfully Submitted,

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[149] 5 U.S.C. § 555(b) ("[W]ithin a reasonable time, each agency shall proceed to conclude a matter presented to it."); *id.* § 706(1) ("The reviewing court shall ... compel agency action unlawfully withheld or unreasonably delayed."); *id.* § 555(e) ("Prompt notice shall be given of the denial in whole or in part of a written application, petition, or other request of an interested person made in connection with any agency proceeding.").