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America's Ethanol Supporters

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Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: **Comments on Draft Guidance for Industry #245, Hazard Analysis and Risk-Based Preventive Controls for Food for Animals; Docket ID: FDA-2018-D-0388-0002**

Dear Associate Commissioner Kux, Director Soloman and Acting Director Murphy:

Growth Energy submits these comments to the Food and Drug Administration (FDA) regarding Draft Guidance for Industry #245, Hazard Analysis and Risk-Based Preventive Controls for Food for Animals (Draft Guidance). Growth Energy represents 99 producers of ethanol who contribute to the industry total production of 44 million metric tons of Dried Distillers Grains with Solubles (DDGS), 83 business associated with ethanol and DDGS production and marketing, and tens of thousands of ethanol supporters across the country.

Growth Energy has two suggestions for improving the Draft Guidance to provide more clarity for regulated persons and reduce the regulatory burden of compliance with Hazard Analysis requirements. These include:

- Clarifying that the listing of hazards associated with products or ingredients in Appendix E is intended to illustrate examples and does not lead to the presumption there is a hazard requiring a preventive control associated with every ingredient or product listed in Appendix E; and

- Removing the listing of antibiotic residue as a known or foreseeable hazard for Dried Distillers Grains with Solubles (DDGS) in Appendix E.

As detailed in our comments below, these modifications to the Draft Guidance will provide regulated establishments greater certainty and will reduce unnecessary regulatory burdens for facilities that process DDGS.

1. **FDA should clarify that the listing of a hazard associated with example products in Appendix E does not lead to a presumption that the example products have a hazard that requires a preventive control**

Chapter 3 of the Draft Guidance is intended to assist establishments in identifying known or reasonably foreseeable biological, chemical, and physical hazards associated with animal food. Chapter 3 is supplemented by Appendix E, "Aid to Identifying Animal Food Hazards." Appendix E contains a list of dozens of example products and identifies hazards FDA asserts are associated with the products. The table also includes a reference to the "evidence" that FDA relies on for asserting that a hazard may be associated with the product.

Many animal food ingredients are amenable to a number of intended uses. There are a wide array of facility designs and operating conditions that have an impact on animal food safety. As such, each facility's hazard analysis will be unique to the particular facility, ingredient, and intended use. The facility's Preventive Controls Qualified Individual (PCQI) is responsible for exercising judgment in determining whether an ingredient poses a known or reasonably foreseeable hazard.

If Appendix E effectively became a presumptive authority on whether an ingredient presents a known or reasonably foreseeable hazard, this would impose an undue burden on regulated facilities and render much of the PCQI's judgment meaningless. If a facility knows that an inspector is going to presume that an ingredient poses a known or reasonably foreseeable hazard, the facility will be required to incorporate the ingredient into the facility's Hazard Analysis, regardless of whether the ingredient *actually* poses a known or reasonably foreseeable hazard.

Growth Energy commends FDA for addressing this question in the March 6, 2018 informational webinar on the Draft Guidance.[1] In the webinar, FDA noted that Appendix E was designed to assist industry by providing a visual illustration of a hazard analysis and FDA inspectors would *not* be trained to rely on Appendix E when evaluating whether a facility had properly prepared its Hazard Analysis.

Growth Energy strongly recommends that the Draft Guidance should be amended to include a statement noting that inspectors are not to rely on Appendix E when evaluating a facility's Hazard Analysis. Otherwise, there is a foreseeable risk that, over time, inspectors will come to rely on Appendix E as a presumption that a particular ingredient poses a known or reasonably foreseeable hazard without evaluating the individual circumstances. Explicitly dispelling the notion of a presumption in the Draft Guidance will ensure this issue does not arise in the future.

2. **FDA should remove the reference to animal drug residue and carryover as a potential hazard for Distillers By-Products (from Fuel Ethanol and Alcoholic Beverage Production)**

Many of Growth Energy's members distill ethanol from corn for use in motor fuel. One of the major co-products of the ethanol production process is DDGS. DDGS add value to the bottom line of ethanol producers and offer a high-protein ingredient for livestock and poultry feeders.

[1] *See* Informational Webinar on FSMA Hazard Analysis and Risk-Based Preventive Controls for Food for Animals Draft Guidance, at approximately 44:00, *available at* https://www.fda.gov/AnimalVeterinary/NewsEvents/WorkshopsConferencesMeetings/ucm598109.htm.

Antibiotics are commonly used in commercial ethanol production facilities to control microbial contamination. Because of the general concerns about antibiotics in animal feed, industry, FDA, and academia have all taken an interest in learning more about the presence of antibiotic residues in DDGS.

Appendix E identifies animal drug residues and natural toxins as examples of known or reasonably foreseeable hazards associated with DDGS. However, Growth Energy strongly objects to the notion that animal drug residue poses a known or reasonably foreseeable hazard in DDGS; thus, this example should be removed from Appendix E in the final version of the Guidance.

FDA's listing of animal drug residues as an example of a known or foreseeable hazard is based on two FDA reports, a 2008[2] and 2010[3] survey of antibiotic residues in distillers products. The reports note that FDA developed an analytical methodology to determine the presence of antibiotic residues. In the 2008 report, the author notes that of the 49 samples tested, antibiotic residues were detected in 28, but quantifiable levels of antibiotic residues were only present in 17 samples. In the 2010 report, which adopted a similar methodology, the author noted that only 4 of the 46 samples yielded quantifiable antibiotic residues. On the basis of the relatively low presence of antibiotic residues in the 2010 report, FDA's Center for Veterinary Medicine indicated that it did not intend to follow up the study with any regulatory action.

Several studies, most of which were published after FDA's 2008 and 2010 reports, dispel the notion that animal drug residues are a reasonably foreseeable hazard associated with DDGS. Growth Energy strongly encourages FDA to take note of the prevailing science on this matter and remove the animal drug residues and carryover example from the listing for DDGS under Appendix E. Otherwise, it is likely that ethanol plants and DDGS handlers will be required to devote time, technical expertise, and financial resources to demonstrate that animal drug residues do not pose a reasonably foreseeable hazard in DDGS.

One example of such a study is the 2013 paper by Paulus Compart, et al.[4] In this paper, the authors analyzed 159 samples of distillers grains for the presence of antibiotic residues and studied whether distillers grains had an active antimicrobial effect. Of these samples, the authors detected antibiotic residues in 12.6% of samples. However, in analyzing microbiological assay, the authors indicated that only one sample inhibited bacterial growth – and that sample did not contain any detectable residues. The authors note that "[d]istillers grains antibiotic residue concentrations observed in the current study, as well as in unpublished FDA surveys, appear to be at concentrations generally considered to be sublethal or they may be biologically inactive."[5] The authors also note that the lack of antimicrobial effect could likely be attributed to antibiotic inactivation that occurs in the high heat/low pH environments that occur during ethanol fermentation. Finally, the Paulus Compart paper concludes that "no direct link

[2] *See* Marla Luther, Ph.D., "Report of FY 2008 Nationwide Survey of Distillers Products for Antibiotic Residues," *available at* https://www.fda.gov/AnimalVeterinary/Products/AnimalFoodFeeds/Contaminants/ucm331189.htm;
[3] *See* Marla Luther, Ph. D., "Report of FY 2010 Nationwide Survey of Distillers Products for Antibiotic Residues," *available at* https://www.fda.gov/AnimalVeterinary/Products/AnimalFoodFeeds/Contaminants/ucm300126.htm.
[4] *See* D.M. Paulus Compart, et al., "Presence and Biological Activity of Antibiotics Used in Fuel Ethanol and Corn Co-Product Production," 91 J. ANIMAL SCI. 2395-404 (2013).
[5] Id. at 2401.

has been shown between use of [distillers grains] in cattle or swine diets and development of bacterial resistance in the gastrointestinal tract of those species."[6]

Furthermore, in a 2015 paper by Manimanna Sankarlal, et al., the authors concluded that both DDGS and milk samples gathered from cows that consumed DDGS did not contain antibiotic residues.[7] In the Manimanna Sankarlal study, the authors sampled DDGS used in dairy rations and milk derived from cows that consumed the DDGS. Their methodology involved testing for the presence of 17 different common antibiotics. Additionally, the study evaluated whether DDGS had any antimicrobial effect against common pathogenic bacteria. The study determined that there were no detectible levels of antibiotics in either the sampled DDGS or milk from cows that consumed DDGS. Moreover, the study determined that the DDGS had no antimicrobial effect on the common pathogens. Finally, the study concluded "[t]he DDGS used in the study will not likely contribute negatively to the health of the cows or to antibiotic resistance in the herd."[8]

A 1999 paper by Islam, et al., also calls into question the amount of antibiotics that remain in distillers products after the fermentation process.[9] This paper demonstrated that the concentration of penicillin dramatically decreases over time during the fermentation process. Specifically, in the Islam study, the penicillin contained in wort was inactivated after 72 hours of fermentation at lower temperatures (25^{o}C), and could be completely inactivated in less than 24 hours in higher temperature environments.[10] Most ethanol fermentations last approximately 70 hours. This paper demonstrates that it is unlikely penicillin would remain active after the fermentation process under real world circumstances.

Growth Energy understands that FDA's chief concern with animal drug residues is the potential risk that it poses to promote the development of antibiotic-resistant bacteria. Growth Energy shares FDA's commitment to ensuring that livestock and poultry feed ingredients marketed by its members is safe and wholesome. Moreover, we are committed to the judicious use of antibiotics. However, the prevailing research has demonstrated that animal drug residues should not be deemed a known or reasonably foreseeable hazard associated with DDGS. The high temperature/low pH fermentation environment typically inactivates antibiotics. As there is no biological activity associated with antibiotic residues in DDGS, there is no environmental pressure that would promote mutations or resistance in bacterial populations. While this is an area where the ethanol producers and DDGS handlers must remain vigilant, it does not rise to the level of concern that warrants a listing under Appendix E.

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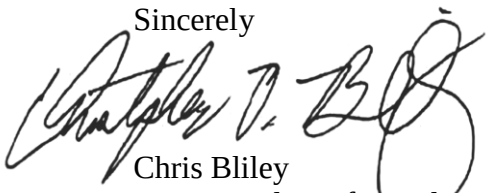
Growth Energy's members are committed to producing safe co-products for its customers in the livestock and poultry industry. We applaud FDA for developing guidance to assist industry in understanding FDA's approach to implementing the Hazard Analysis and Preventive Controls portion of FSMA. However, we believe there is room for improvement in the Draft Guidance that will reduce regulatory burdens without impacting food safety. First, FDA should explicitly clarify that Appendix E is

[6] Id. at 2402.
[7] *See* V. Manimanna Sankarlal, et al., "*Short Communication*: No Antimicrobial Effects From One Source of Commercial Dried Distillers Grains with Solubles," 98 J. DAIRY SCI 8554-59 (2015).
[8] Id. at 8558.
[9] *See* M. Islam, et al., "Stability of Virginiamycin and Penicillin During Alcohol Fermentation," 17 BIOMASS AND BIOENERGY 369-76 (1999).
[10] Id. at 373-75.

to serve as an illustrative example, and not a presumption that particular ingredients pose a known or reasonably foreseeable hazard. Second, animal drug residue and carryover should not be listed as an example of a known or reasonably foreseeable hazard associated with DDGS.

Thank you in advance for your consideration of our comments.

Sincerely



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