DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

OCT 0 1 2012

The Honorable Louise M. Slaughter
House of Representatives
Washington, D.C. 20515-3228

Dear Ms. Slaughter:

Thank you for your letter of May 11, 2012, cosigned by Representative Edward J. Markey, expressing your concern that the use of antibiotics in corn-based livestock feed may be contributing to the development of antibiotic-resistant bacteria and subverting FDA's efforts to ensure the judicious use of antibiotics in food-animals.

By way of background, distillers' products, including distillers' grains (DG), have a long history of use as an animal feed ingredient. Distillers' products are the co-products of the fermentation process used in the production of fuel from the dry mill fuel or beverage ethanol process and are obtained after the removal of ethyl alcohol by distillation from the yeast fermentation of a grain or grain mixture. Although the use of DG as an animal feed ingredient was in the past fairly limited, FDA has focused greater scrutiny on this practice as its use as a livestock feed ingredient has increased.

We have restated your questions below in bold, followed by our responses.

1. **Why hasn't the FDA published the full results of the 2008 survey of antibiotic residues in DGS? Are the full results of the 2008 survey publically available? If so, where? If not, why not?**

   The Agency conducted surveys in 2008 and 2010 in which samples were collected from domestic ethanol processors to determine the extent and level of antibiotic residues in DG. The samples were considered investigational samples intended for use for research purposes and to support FDA's ongoing effort to develop policy in this area.

   FDA's 2008 survey involved the collection and analysis of 45 DG samples for residues of 12 antibiotics (ampicillin, penicillin G, chlortetracycline, oxytetracycline, tetracycline, clarithromycin, erythromycin, streptomycin, virginiamycin M_1, bacitracin A, chloramphenicol, and tylosin) and one non-antibiotic antimicrobial (monensin), using the method found in Laboratory Information Bulletin (LIB) 4438. At the time of these analyses, that method had not yet been validated. Preliminary results showed antibiotic residues were detected in 24 of the samples, with the most prevalent being virginiamycin (15 samples), erythromycin (8 samples), and tylosin (5

samples). Of the preliminary analyses, the maximum residues found on a dry weight basis were 2.9 ppm erythromycin, 0.17 ppm tylosin, and 0.49 ppm virginiamycin.

Subsequent to conducting the 2008 survey, FDA completed the validation of the analytical method and published the method in its LIB in July 2009. For additional information on the validated FDA analytical method used to detect antibiotic residues in the DG samples, see LIB 4438, "Analysis of Antibiotics in Distillers Grains Using Liquid Chromatography and Ion Trap Tandem Mass Spectrometry."[1]

FDA's 2010 survey included the collection of a total of 46 DG samples. FDA laboratories analyzed the 46 samples for residues of the same 12 antibiotics and monensin, using the now-validated method found in LIB 4438. FDA's final analysis found that four of the 46 samples analyzed contained antibiotics that were above the level of quantification. These four samples contained a total of five antibiotic residues. Of the three positive analyses of domestic products, the residues found were approximately 0.58 ppm erythromycin, 0.24 ppm penicillin, and 0.15 ppm virginiamycin on a dry weight basis. The one positive sample imported from Canada contained approximately 0.18 ppm virginiamycin. (The limit of quantification using the LIB 4438 method is 0.1 ppm for virginiamycin M_1, 0.5 ppm for erythromycin, and 1.0 ppm for penicillin.)

Although the full results of the 2008 survey of antibiotic residues in DG were not published, the results were compiled and presented at the 13th Annual National Ethanol Conference in February 2008 and the 13th Annual Distillers Grains Symposium in April 2009. The results of the 2010 survey were presented in a poster at the 34th Symposium on Biotechnology for Fuels and Chemicals held April 30 – May 3, 2012, and a report on the results is available on the Agency's website.[2] FDA also intends to post a report on the results of the 2008 survey later this year.

2. **Did the information collected by the FDA in its survey of antibiotic residues in DGS suggest that drug contamination may pose a risk to animals used for human consumption? Are these antibiotic residues found in meat or poultry products? Are these residues found in milk and eggs? Please provide the full results of studies in which residues of DGS were surveyed.**

The information collected by FDA in the 2008 and 2010 surveys did not suggest that drug contamination poses a risk to animals used for human consumption, but the data from those surveys are limited in both number and scope. As part of the new animal drug approval process, FDA previously reviewed the safety to animals of the four antibiotics that were found in the DG samples (erythromycin, penicillin, virginiamycin, and tylosin) and determined that the substances, even at the much higher rates used in medicated feed, do not provide an animal safety concern in the species for which the drugs are approved.

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[1] *http://www.fda.gov/downloads/AnimalVeterinary/ScienceResearch/ToolsResources/UCM182280.pdf*

[2] *http://www.fda.gov/AnimalVeterinary/Products/AnimalFoodFeeds/Contaminants/ucm300126.htm*

That being said, we do not have target animal safety information for those species in which the substance has not already been approved as part of a new animal drug application. For example, virginiamycin is not approved for use in laying hens. Additionally, we do not have any information about drug interactions that might occur if DG with residues of antibiotics are mixed with medicated feed, if those combinations of drugs have not previously been reviewed by FDA as part of a new animal drug application.

FDA has not conducted a study to evaluate possible residues found in meat, poultry, milk, or eggs as a result of antibiotic residues in DG. When FDA reviews petitions under the food additive petition (FAP) review process, it will evaluate the potential target animal safety and human food safety concerns, including, but not limited to, the ones listed above.

In response to your request, the analytical results of the 2008 and 2010 surveys are enclosed in separate spreadsheets.

3. **Does FDA believe that the presence of antibiotics in DGS used for livestock feed may pose a similar public health concern as the impact of directly using antibiotic drugs to promote livestock growth? Please fully document your response.**

More information is needed to determine whether the presence of antibiotic residues in DG used for livestock feed may pose some similar public health concerns as the impact of directly using antibiotic drugs to promote livestock growth. The Agency does have some preliminary data from studies conducted by FDA's Center for Veterinary Medicine. That group analyzed the DG samples that tested positive for residues and conducted low-level exposure studies to look for changes indicative of antibiotic resistance. Specifically, they found that low levels of virginiamycin (0.1 ppm and 1.0 ppm) and penicillin (1.0 ppm) did not select for resistant variants of indicator species of gastrointestinal tract bacteria (*Enterococcus sp.* and *Campylobacter sp*); however, low levels of erythromycin (0.5 ppm) did select for resistant variants. They did not study the impact of higher levels of these antibiotics. This information was presented in a poster at the 34th Symposium on Biotechnology for Fuels and Chemicals held April 30 – May 3, 2012. This study ("Impact of low level antimicrobial residues in distillers' grains") reported that the presence of low levels of virginiamycin and penicillin did not result in the development of antibiotic resistance in selected strains of *Enterococcus sp* and *Campylobacter sp.*

As part of the FAP process, FDA will review additional information, including but not limited to, the antibiotics' use rate, degradation during fermentation, post-distillation degradation such as drying, bioavailability, and residues in edible tissues to evaluate whether there is a public health concern from residues of antibiotics in DG used in or as food for food-producing animals.

4. **A report by the IATP presents FDA's position that antibiotics in DGS are considered Food Additives and are therefore subject to regulations under the Federal Food, Drug and Cosmetic Act, but that industry rejects this view. What is FDA doing to ensure that ethanol producers are complying with Food Additive Regulations? If FDA is not taking any action to ensure compliance or if FDA has changed position regarding the need to comply with Food Additive regulations, please provide a clear explanation.**

   The Federal Food, Drug, and Cosmetic Act gives FDA the authority to regulate additives in food, including food for animals. If a component of food meets the definition of a food additive, it must be approved by FDA before it can be legally marketed. In addition, its use must meet the conditions stated in a food additive regulation that FDA publishes when it approves the food additive. Conversely, if a component of food is considered generally recognized as safe (GRAS), FDA premarket approval is not required.

   Because there are no premarket approval requirements for GRAS ingredients, companies lawfully can introduce into commerce GRAS ingredients without first seeking FDA authorization to do so. To meet the "general recognition" component of GRAS, the data and information relied on to establish the safety of the substance must be generally available, and there must be a basis to conclude that there is consensus among qualified experts about the safety of the substance for its intended use.

   Since 2007, the Agency has been providing information to fuel ethanol producers, ingredient (antibiotic) suppliers, and users of DG regarding their responsibility to produce a safe animal food ingredient. In addition, as part of FDA's outreach to animal food ingredient suppliers, animal food manufacturers, and the public, FDA posted a letter on its website explaining that when a food substance is marketed as GRAS, it does not necessarily mean that FDA has reviewed or concurred with the regulatory status of the substance [see, "Letter to Industry: Marketing of Animal Food Substances as Generally Recognized As Safe (GRAS)" on the FDA Animal and Veterinary webpage[3]].

   In addition, FDA has published notices in the *Federal Register* announcing that four food additive petitions for antibiotic processing aids in ethanol production have been submitted for review. These include one petition for the use of virginiamycin, one petition for the use of penicillin, and two petitions for the use of erythromycin thiocyanate. FDA has reviewed the information in the petitions and sent letters to the petitioners describing the additional information that is necessary to evaluate the safety of the antibiotics for this use.

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[3] *http://www.fda.gov/AnimalVeterinary/Products/AnimalFoodFeeds/GenerallyRecognizedasSafeGRASNotifications/default.htm*

5. **Why did FDA choose to ban the use of DGS contaminated with the antibiotic, virginiamycin, in laying hens, but not in other food-producing animals? Please fully document your response.**

FDA had previously stated that it did not object to the use of virginiamycin in the fermentation phase of alcohol production. This was based on an expected-use level of virginiamycin at 2-6 ppm in the production process and a residue in DG intended to be used in or as animal feed of between 0.2 and 0.5 ppm of virginiamycin. FDA did not limit this statement to use of DG containing virginiamycin to any particular animal species. However, in response to a specific industry inquiry about the use of DG in feed for layers, FDA said that DG containing detectable levels of virginiamycin residues from use of the antibiotic in the fermentation of alcohol production would not be considered acceptable for use. This statement was based on the fact that virginiamycin, while approved for use as a new animal drug for some species, had not been reviewed or approved for use in layers, and no tolerance had been set for any residues in eggs.

Thank you, again, for contacting us concerning this matter. If you have any further questions or concerns, please let us know. The same letter has been sent to your cosigner.

Sincerely,

Jeanne Ireland
Associate Commissioner
for Legislation

Enclosures

FY 2008 Nationwide Survey of Distillers Products for Antibiotic Residues

FACTS #	type	LOD, %	Virginiamycin, ppm		Erythromycin, ppm		Dehydro-ERY, ppm		Tylosin, ppm	
				as is		as is		as is		as is
223716	D	12								
300218	D	12								
343564	D	12					C	< 0.1		
393387	D	12								
395250	D	10					T	< 0.1	T	< 0.1
395251	D	12	C	0.2						
418517	W	73								
418518	W	76								
418519	W	68			T	0.3	C	0.6		
418520	D	12			C	1.3	C	1.3		
432276	D	12								
432278	W	59								
432280	S	76								
432281	S	73								
432282	W	66								
436665	W	63	C	0.2						
436667	D	12	C	0.3						
443619	W	70								
443623	W	58								
443624	S	51								
443626	D	12			C	1.1	C	1.5	T	< 0.1
443627	D	11			T	0.9	C	1.3		
443630	D	12	T	< 0.1			C	0.4		
443640	S	71							T	< 0.1
443641	D	11							T	< 0.1
451489	D	14								
451492	D	12								
451792	D	9	C	0.2						
454188	W	66								
466611	D	12	T	< 0.1						
466619	D	12	C	0.3						
468911	W	51	C	0.3						
468912	D	12	C	0.4						
472483	D	12								
476471	D	14					C	0.1		
478612	D	10	C	< 0.1						
478615	D	12								
478618	D	12								
478621	D	13	T	0.1					T	< 0.1
479264	D	12								
479873	W	68								
483011	D	15	T	0.1						
483011	W	67	T	< 0.1						
483393	W	63	C	0.3						
483394	W	59	C	0.3						

D = dry
W = wet
S = stillage

C = confirmed
T = tentative

FY 2010 Nationwide Survey of Distillers Products for Antibiotic Residues

Sample ID	Antibiotic	Amount (mg/kg)	% Moisture	% Solids	Moisture Correction Factor	Residue Level on Dry Weight Basis (mg/kg)
590771	Virginiamycin M	0.106	0.86	99.14	1.01	0.11
530950	Virginiamycin M	0.144	7.12	92.88	1.08	0.16
457537	Virginiamycin M	0.176	1.28	98.72	1.01	0.18
451372	Virginiamycin M	0.141	4.85	95.15	1.05	0.15
444488	Erythromycin	0.499	13.9	86.1	1.16	0.58
451372	Penicillin-G	0.173	4.85	95.15	1.05	0.18

Product Code	INV #	District Office	ABx information LC-MS/MS (LIB 4438) (Limit of Quantification (LOQ) = 0.2 ppb)	Comments
71FYB02	**385615**	DET	No Abx detected @ 0.2 ppb Moisture content = 0.60%	Dried Distillers Grains with Solluables (DDGS) (from corn Sample collected from bulk cylindrical tank, 76000 lbs.
71FYB99	**424170**	KAN	No Abx detected @ 0.1 ug/g Erythromycin (ERY) could not be determined Moisture content = 0.86%	DDGS from corn (BUNGE) Abx used: lactrol Abx added: fermenter
70YY_99	**444488**	DET	ERY as dehydro = 0.05ug/g Other Abx not detected Moisture content = 13.9%	DDGS from corn Abx used: fermguard xtreme (ERY) Abx added: yeast prop and fermenter
71FYH99	**451372**	DET	Virginiamycin (VIR) detected @ 0.141 ug/g Penicillin (PEN) detected @ 0.173 ug/g Moisture content=4.85%	DDGS from corn Abx used: lactrol Abx added: fermenter and yeast tank
71FYB02	**457537**	NYK	VIR detected @ 0.2 ppb Moisture content = 1.28%	DDGS from corn Abx used: virginiamycin Abx added: fermenter
71FYH02	**481040**	NYK	No Abx detected @ 0.2 ppb Moisture content = 0.88%	DDGS from corn Abx used: lactrol Abx added: fermenter and yeast tank
70AY_02	**527059**	KAN	No Abx detected @ 0.1-0.6 ug/g Moisture content = 6.07%	Corn Gluten Feed (corn whole/ground grains)
71FYB02	**530950**	KAN	VIR detected @ 0.144 ug/g Moisture content = 7.12%	Dried Distillers Grains (DDG) form corn Abx used: lactrol
71FYB02	**532539**	KAN	No Abx detected @ 0.1 ug/g Bacitracin not detected @ 0.26 ug/g Moisture content = 1.08%	DDG form corn Abx used: lactrol
70YY-99	**552233**	KAN	No Abx detected @ 1ppm Moisture content=65.5%	Wet Distillers Grains (WDG) from corn Abx used: VIR (lactrol) Abx added: fermenter
71FYN02	**562666**	SEA	No Abx detected @ 0.1 ug/g Moisture content = 9.67%	WDG from corn: 70% moisture Abx used: Bactinex V50 and Lactrol Abx added: yeast tank and fermenter
71FY_99	**564428**	NYK	No ERY, VIR or tylosin detected above LOQ (NRL)	DDGS Abx used: allpen (PEN G @60g/64 metric tons) Abx added: fermenter
71YYY99	**575594**	LOS	No Abx detected @ 1ppm Moisture content=85.4%	Liquid protein concentrate (salvaged/distressed) No Abx added - but unknown what is in feedstock
71FYB02	**577204**	NYK	No Abx detected @ 0.2 ppb Moisture content = 0.60% and 1.11%	DDGS from corn
71FYB99	**578267**	NYK	No Abx detected @ 0.1 ug/g Moisture content = 0.86%	DDGS from corn
71FYB02	**578278**	NYK	No Abx detected @ 0.2 ppb Moisture content = 1.65%	DDGS from corn

71FYB02	**578581**	NYK	No Abx detected @ 0.2 ppb Moisture content = 1.65% and 0.68%	DDGS from corn
71FYY02	**580129**	NYK	No Abx detected @ 0.2 ug/g Moisture content = 0.78%	DDGS from wheat
71FYB02	**581987**	DET	No Abx detected @ 0.2 ppb Moisture content = 1.02%	DDGS from corn
71FYB02	**583367**	DET	No Abx detected @ 0.2 ug/g Moisture content = 25 %	WDGS from corn
70AY 02	**585510**	CIN	No Abx detected above LOQ Moisture content = 1.23%	DDG from corn Abx used: Penicillin G Procaine Vet Grade Abx added: yeast prop tank
71FYH99	**585984**	DET	No Abx detected @ 0.1 ug/g Moisture content = 0.67%	DDGS from corn Abx used: FermGuard Xtreme (ERY, 2ppm in prop tank) FermGuard (Ampicillin/BetaLactam, 2ppm in prop tank)
71FYN02	**587502**	KAN	No Abx detected above LOQ Moisture content = 46.5%	WDG from corn Abx used: Bactinex V50
71FYN02	**587503**	KAN	No Abx detected above LOQ Moisture content = 8.82%	DDG from corn Abx used: Bactinex V50
71 FYN02	**588074**	SEA	No Abx detected above LOQ Moisture content = 10.15%	WDG from corn: 70% moisture Abx used: rotate between Bactinex V60 (PEN) and Lactrol (VIR) Abx added: fermenter
71FYH02	**590771**	CHI	No Abx detected at LOQ VIR = 0.106 ug/g Moisture content = 0.86%	DDGS from corn Abx used: lactrol (VIR) Abx added: pre-fermenter in tempering tank
71FYY99	**590935**	SEA	No Abx detected @ 0.1 ug/g No TC detected @ 1.1 ug/g Moisture content = 0.70%	DDG from wheat Abx used: VIR (lactrol, lactoside V, lactoside 247, Bactinex 50)
70AY 02	**594900**	KAN	No Abx detected at LOQ Moisture content = 5.64% No animal protein detected	Brown colored bulk ground product
71GYY99	**597755**	"NWE"	No Abx detected @0.1 ug/g Moisture content = 0.82%	DDG from corn
71FYB99	**600464**	KAN	No Abx detected at LOQ Moisture content = 1.13%	DDGS from corn Abx used: Bactinex V300 (ERY/Dextrose)
71FYB99	**600474**	KAN	No Abx detected @ 0.1 ug/g No bacitracin detected @ 0.26 ug/g Moisture content = 0.78%	DDGS from corn Abx used: chlorine dioxide
71FYB99	**600477**	KAN	No Abx detected @ 0.1 ug/g No bacitracin detected @ 0.26 ug/g Moisture content = 1.5%	DDGS from corn
71FYB99	**600480**	KAN	No Abx detected @ 0.1 ug/g No bacitracin detected @ 0.26 ug/g Moisture content = 0.83%	DDGS from corn Abx used: none
71FYH02	**603115**	CHI	No Abx detected @ 0.1 ug/g No TC detected @ 0.55 ug/g No bacitracin detected @ 0.26 ug/g Moisture content = 0.65%	DDGS from corn Abx used: none

71FYB02	**605369**	KAN	No Abx detected @ 0.1 ug/g No bacitracin detected @ 0.26 ug/g Moisture content = 1.60%	DDGS from corn Abx used: lactrol and lactoside 247 (VIR/PEN) Abx added: fermentation tank
71FYY99	**607769**	DAL	ERY as dehydro = 1.09ug/g Other Abx not detected Strep not determined Moisture content = 6.08%	WDG from milo Abx used: FermGuard Xtreme (ERY) Abx added: prior to fermentation
71FYH99	**625990**	DET	Abx were not detected Moisture content = 4.9%	DDGS from corn Abx used: lactrol, lactoside V, lactoside 247, neotrol
71FYB02	**629159**	KAN	Abx were not detected Strep not determined Moisture content = 0.8%	DDGS form corn Abx used: lactrol Abx added: fermentation tank
71FYB02	**629162**	KAN	No Abx detected at LOQ Moisture content = 9.9%	DDGS from corn Abx used: Bactinex V300 (ERY), V60 (PEN) Abx added: Fermentation tank
71FYY99	**633235**	SEA	No Abx detected at LOQ Moisture content = 8.9%	DDG
71FYY99	**635851**	SEA	No Abx detected at LOQ Moisture content = 8.9%	DDG
71FYH02	**636730**	CHI	Abx not detected @1ppm Moisture content=11.0%	DDGS from corn Abx used: VIR Abx added: fermenter
70AY_02	**642532**	CIN	Abx not detected @1ppm Moisture not reported	DDGS Abx used: lactrol Abx added: yeast prop, slurry tank
71FYY99	**645158**	SEA	Abx not detected @1ppm Moisture content=10.8%	DDG
71FYY99	**646310**	SEA	Abx not detected @1 ppm Moisture content=9.4%	DDG
71FYY99	**656714**	SEA	Antibiotics not detected at or above the LOQ	DDG
Samples Provided but Not Part of the Survey				
70YY_99	569840	BLT	No monensin detected (above 0.5 ug/g)	Inactivated yeast Test for monensin
71FY_99	571755	ATL	No monensin detected (above 1 ug/g)	Yeast cell wall Test for monensin
71FYY99	592967	BLT	No monensin @ 1 ppm	Dried brewers yeast Test for monensin
71FYY99	592984	BLT	No monensin @ 1 ppm	Dried brewers yeast Test for monensin
71FYH99	598369	DEN	No monensin @ 1 ppm	Inactivated yeast Test for monensin