conditions;[35] the NADA must also be denied if the Secretary finds that there is "insufficient information to determine whether such drug is safe for use under such conditions."[36] Section 512 also lays out the conditions under which a previously granted NADA is to be withdrawn, i.e., if the Secretary finds that the drug is "**unsafe**" for use under the approved conditions, or if evidence "**shows that such drug is not shown to be safe**" for such use.[37]

Thus, the legal and public health standard for granting and withdrawing NADA approvals are substantively identical, i.e., if a use is either shown to be "unsafe" or is "not shown to be safe."

In Guidance #152, FDA states that it considers an agricultural antibiotic to be "safe" if the agency "concludes that there is reasonable certainty of no harm to human health from the proposed use of the drug in food-producing animals." While Guidance #152 was initially directed at drug producers seeking approval to market additional drugs, the Guidance's criteria apply equally to existing NADAs for drugs now on the market, given that there is no scientific or legal distinction between standards for approval and standards for withdrawal.

As a practical matter, in withdrawing a drug FDA must "provide a reasonable basis from which serious questions about the ultimate safety [of a drug] may be inferred."[38] Such questions "can be raised where the evidence is not conclusive, but merely suggestive of an adverse effect."[39] Once an initial showing of "serious questions" is made, the burden shifts to the drug manufacturer to establish that the use in question is "shown to be safe."[40]

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[35] FDCA § 512(d)(1)(A) & (B), 21 U.S.C. § 360b(d).
[36] FDCA § 512(d)(1)(D), 21 U.S.C. § 360b(d).
[37] FDCA § 512(e), 21 U.S.C. § 360b(e) (emphasis added). Implementing regulations parallel the language of the statute. 21 C.F.R. § 514.115(b). The relevant text of section 512(e) reads as follows:

> (1) The Secretary shall, after due notice and opportunity for a hearing to the applicant, issue an order withdrawing approval of an application filed pursuant to subsection (b) of this section with respect to any new animal drug if the Secretary finds—
> (A) that experience or scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved ...;
> (B) that new evidence not contained in such application or not available to the Secretary until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to the Secretary when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved . . . .

[38] Proposal to Withdraw Approval of the New Animal Drug Application for Enrofloxacin for Poultry, docket no. 00N-1571. Initial Decision of March 16, 2004, at p. 5. Available at www.fda.gov/ohrms/dockets/dailys/04/mar04/031604/00n-1571-idf0001-vol389.pdf (accessed Apr. 5, 2005). Fluoroquinolones are **not** approved for use as feed additives, and this Petition **does not** cover use of fluoroquinolones.
[39] Ibid., p. 5 (embedded quotation marks and citations omitted).
[40] Ibid., p. 7.

b. The Criteria in Guidance #152 Are Applicable to Existing Approvals for Agricultural Antibiotics Now on the Market

As FDA noted in its Press Release on Guidance #152, the Guidance is "the first [document] that addresses, in a comprehensive manner, the issue of the use of antimicrobials in food producing animals as a contributing factor to the development of antimicrobial resistance."[41] Although the Guidance on its face applies only to *future* applications for approval of antimicrobials rather than to drugs already on the market, the 2003 Annual Report for FDA's Center for Veterinary Medicine states that the Guidance's "principles will also be applied in determining whether to remove approved products from the market."[42] In addition, FDA's Federal Register notice for the Guidance states "The guidance represents the agency's current thinking about the safety of [agricultural-animal] drugs, with regard to their microbiological effects on bacteria of human health concern."[43]

As demonstrated in the following section of this Petition, applying the Guidance's criteria to the petitioned drug uses indicates that those uses are inconsistent with the Guidance. As a result, "serious questions" clearly exist with regard to the safety of these uses. Accordingly, FDA should promptly initiate and conclude the process of withdrawing those uses.[44]

4. The Antibiotic Uses Covered by this Petition Are Not Consistent with the Criteria in Guidance #152

Format Note: The following discussion includes several excerpts of tables that are taken verbatim from Guidance #152. Those excerpts are shown in this typeface. The excerpts are identical to the Guidance except as noted by use of brackets; in addition, some footnotes have been omitted.

a. Overview

Guidance #152 lays out FDA's recommended approach to evaluating the safety of agricultural antibiotics with regard to creation of antibiotic-resistant bacteria of human health concern. Although the Guidance in several places uses terms such as "suggested" or "examples" of approaches, this Petition focuses on the substantive content of the

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[41] FDA, "FDA Issues Guidance on Evaluating the Safety of Antimicrobial New Animal Drugs to Help Prevent Creating New Resistant Bacteria" (press release), Oct. 23, 2003. Available at www.fda.gov/bbs/topics/NEWS/2003/NEW00964.html (accessed Apr. 5, 2005).

[42] U.S. Department of Health and Human Services, Food and Drug Administration, Center for Veterinary Medicine. Annual Report – Fiscal Year 2003 (October 1, 2002 - September 30, 2003), p. 20. Available at www.fda.gov/cvm/Documents/CVMFY03AnnRpt.pdf (accessed Apr. 5, 2005).

[43] 68 Fed. Reg. 61221 (Oct. 27, 2003). Available at www.fda.gov/OHRMS/DOCKETS/98fr/03-27113.pdf (accessed Apr. 5, 2005).

[44] As noted above, withdrawals for certain uses of some drugs were initiated in the 1970s and remain pending. See Appendix 3.

Guidance, as indicating FDA's best thinking on how these analyses should be performed, and on how identified risks should be managed to avoid unsafe outcomes.

Under the Guidance, use of a particular drug is assigned an overall "risk estimate" of High, Medium, or Low based on a qualitative risk assessment that has three components: release, exposure, and consequence.

- Release. How likely is the drug to be used in food animals in a way that engenders resistance?
- Exposure. How likely are the resistant organisms to make their way to humans?
- Consequence. How important are the drugs for human medicine?

In addition, the Guidance lays out a mechanism for integrating the results of these three assessments into an overall qualitative risk estimate of High, Medium, or Low.

The Guidance also describes risk management steps associated with high, medium, and low risks findings. Among others, these risk management steps include limitations on the extent of use (e.g., individual animal vs. herdwide/flockwide use).

Because this Petition addresses certain already-approved uses, it is convenient to start by considering the Guidance's risk management strategies, before examining the components of the qualitative risk analysis. The following section presents an analysis of these provisions for the uses covered by this Petition.

b. Guidance #152 Allows Herdwide/Flockwide Use Only for "Low Risk" Antibiotics

Table 7 (p. 23) describes high "extent of use" as all flock-wide and herd-wide use, regardless of duration:

Table 7 (excerpt)

Duration of use	Intended administration to:		
	individual animals	select groups or pens of animals	flocks or herds of animals
Short (<6 days)	L[1]	M[2]	H[3]
Medium (6-21 days)	L	M	H
Long (>21 days)	M	H	H

[1]Low, [2]Medium, and [3]High extent of use

Next, Table 8 (p. 25) indicates that a "high" extent of use is *only* allowable for drugs that fall in Category 3 because they have a Low risk ranking; by contrast, "high" extent of use is *not* allowable for drugs in either Category 1 (High risk) or Category 2 (Medium risk):

Table 8 (excerpt)

Approval conditions	Category 1 (High)	Category 2(Medium)	Category 3 (Low)
Extent of use[2]	Low	Low, medium	Low, medium, high

[2]See Table 7 for characterization of extent of use

In summary, herdwide/flockwide use is allowable *only* for drugs with a Low risk ranking. As shown in the following section, the drugs covered by this Petition are not Low risk. Accordingly, their flock- or herd-wide use is inconsistent with the Guidance's safety criteria.

c. The Antibiotics Covered by the Petition are Not "Low Risk"

Under the Guidance, a Low risk ranking occurs *only* under certain circumstances. As noted above, risk rankings are produced by integrating three separate qualitative assessments – "Release," "Exposure," and "Consequence." "Consequence" means the importance of the drug in human medicine, and may be rated as Important, Highly Important, or Critically Important. As further discussed below, "Exposure" describes the likelihood of people to be exposed to antibiotic-resistant bacteria from food, and is rated as High, Medium, or Low; "Release" involves whether agricultural use of the drug selects for resistant bacteria in the animal, and is also rated as High, Medium, or Low.

As shown below, the Release evaluation does not affect the overall Risk ranking for the drugs and uses covered by this Petition; in other words, the Consequence and Exposure evaluations alone will determine the outcome. To demonstrate this, it is useful to look first at the Consequence evaluation, then the Exposure evaluation, and then to consider how the two combine for the final Risk rating.

The Guidance defines drugs' importance in human medicine as "critically" or "highly" important as follows (Table A1, pp. 30-33):

> **Critically Important:** Antimicrobial drugs which meet BOTH criteria 1 and 2 below.
>
> **Highly Important:** Antimicrobial drugs which meet EITHER criteria 1 or 2 below.
>
> 1. ***Antimicrobial drugs used to treat enteric [gut] pathogens that cause food-borne disease.***

2. *Sole therapy or one of few alternatives to treat serious human disease or drug is essential component among many antimicrobials in treatment of human disease.*[45]

As shown in the following excerpt from the Guidance, the drugs covered by this petition all are ranked as "critically important" or "highly important." Specifically, macrolides are "critically important," while penicillins, aminoglycosides, clindamycin/lincomycin,[46] tetracyclines, glycopeptides, and streptogramins are "highly important." One sulfonamide combination drug – namely trimethoprin/sulfamethoaxole[47] – is also designated as critically important (see discussion in section IV.C. below).

Table A1 (excerpt)

	Classification	1) Enteric pathogen responsible for food-born disease	2) Sole/limited therapy or essential therapy for serious disease (See "Comments" for examples)	3) Used to treat enteric pathogens in non-food-borne disease	4) No cross-resistance within class/no linked cross-resistance with other classes	5) Limited risk of transmission of resistance elements within/across species of organisms	Comments
Natural penicillins	H		X				Neurosyphilis: Serious infection due to Group A streptococci
Benzathine pen G							
Penicillin G							
Penicillin V							
Penase Resistant Pens	H		X				Serious infections due to *Staphylococcus aureus*
Cloxacillin							
Dicloxacillin							
Nafcillin							
Oxacillin							
Antipseudomonal Pens	H		X	X			Serious infections due to *Pseudomonas aeruginosa*
Mezlocillin							
Pipercillin							
Pipercillin/tazo							
Ticarcillin							
Ticarcillin/Clav							

[45] In Petitioners' view, this criterion is insufficiently protective of the public health, inasmuch as it fails to protect valuable drugs simply because there are more than a "few" alternative drugs at present. Given that resistance to existing antibiotics is spreading far more rapidly than new drugs are being developed, this approach is unwise. For purposes of this Petition, however, we employ the Guidance's categorization of drugs.

[46] Table A1 lists clindamycin, which is essentially identical to lincomycin. Clindamycin is the primary form of the drug used in humans, while lincomycin is primarily used in animals. The two drugs differ by a single group: a hydroxyl group (OH) in lincomycin is substituted by a chlorine (Cl) in clindamycin. See "Antimicrobial Chemotherapy," www.bmb.leeds.ac.uk/mbiology/ug/ugteach/icu8/antibiotics/protein.html (accessed Apr. 5, 2005).

[47] Guidance #152 uses the abbreviation "trimeth/sulfameth." See Table A1.

Carbenicillin							
Aminopenicillins	H		X	X			Infections due to *Listeria monocytogenes*
Amoxicillin							
Ampicillin							
Ampicillin/Sulbacta							
Aminoglycosides	H		X	X			
Amikacin							
Gentamicin							Enterococcal endocarditis
Tobramycin							Sole antimicrobial approved for aerosolized therapy in cystic fibrosis
Kanamycin							
Streptomycin							Infections due to *Mycobacterium tuberculosis*
Neomycin							
Netilmicin							
Spectinomycin							Infections due to *Neisseria gonorrhoeae* in pregnancy
Macrolides	C	X	X				Legionnaire's disease: MAC/MAI prophylaxis and therapy
Erythromycin							
Azithromycin							
Clarithromycin							
Clindamycin [Lincomycin]	H		X				Serious infections due to Group A streptococci: Alternative therapy of infections due to *Staphylococcus aureus* in patients with serious beta lactam allergy
Tetracyclines	H		X				Rickettsial disease: Anthrax therapy/prophylaxis
Tetracycline							
Chlorteracycline							
Demeclocycline							
Doxycycline							
Minocycline							
Glycopeptides	H		X				Infections due to methicillin resistant *Staphylococcus aureus*
Vancomycin							
Streptogramins	H		X				Infections due to vancomycin resistant *Enterococcus faecium*
Dalfopristin/quinupristin							
Trimeth/Sulfameth	C	X	X	X			Infection due to *Pneumocystis carinii*

The next key factor is found in Table 6 of the Guidance (p. 21), which provides a grid of all possible combinations of the three assessments' ratings and the resulting risk ranking. Significantly, Table 6 indicates that Critically Important drugs *never* receive a Low risk

ranking, while Highly Important drugs receive a Low risk ranking *if and only if* the Exposure and Release rankings are *both* Low.

Table 6 (excerpt)

Release	***Exposure***	***Consequence***	***Risk Estimation***
Low	Low	Highly important	Low
[Medium or High]	[Medium or High]	Highly important	[Medium or High]
[any]	[any]	Critically Important	[Medium or High]

The Exposure rating is a function of two factors: level-of-consumption and extent-of-contamination (p. 19).[48] Table 2 (p. 17) indicates that consumption of beef, chicken, and pork qualifies as a "High" consumption commodity:

Table 2 (excerpt)

Commodity	***Per capita* consumption (pounds per capita per year)**	**Qualitative ranking**
Beef	62.9	High
Chicken	53.9	High
Pork	46.7	High

The probability of exposure is then determined from Table 5. Under Table 5, if the amount of a food commodity consumed is High, the probability of exposure is always High or Medium (never Low), regardless of extent of contamination of the food commodity:

Table 5

	Probability of human exposure to a given bacteria		
	Amount of food commodity being consumed		
Amount of food commodity contamination	**High**	**Medium**	**Low**
High	H	H	M
Medium	H	M	L
Low	M	L	L

[48] The Guidance's exposure evaluation ignores all non-food pathways, though the Guidance notes in passing that "uncertainties regarding the contribution of other exposure pathways may be considered during the development of appropriate risk management strategies" (p. 15). The Petitioners view the disregard of non-food pathways as another way in which the Guidance is less-than-protective of public health. For purposes of this Petition, however, we employ the Guidance's exposure evaluation scheme, because the uses covered by this Petition are nonetheless inconsistent with even those less-than-protective criteria.