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Food and Drug Administration  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852

RE: Docket No. 98D-1146, CVM 200132

(Also submitted electronically to <http://www.fda.gov/dockets/ecomments>, No. 98D-1146)

This document sets forth the comments of Environmental Defense on FDA's September 6, 2002, draft document titled "Draft Guidance for Industry: Evaluating the Safety of Antimicrobial New Animal Drugs With Regard to Their Microbiological Effects on Bacteria of Human Health Concern" (67 Fed. Reg. 58058-58060 (Sept. 13, 2002), [www.fda.gov/OHRMS/DOCKETS/98fr/98d-1146-gdl0001.doc](http://www.fda.gov/OHRMS/DOCKETS/98fr/98d-1146-gdl0001.doc)).

**Summary.** Although Environmental Defense views the draft Guidance as a useful step forward, we are concerned about several points. Chief among these are the following:

1. *Reviews of existing approvals.* The document lacks a clear commitment to expeditiously review already-approved antibiotics, particularly those that are both important in human medicine and used agriculturally in substantial quantities. Nor is there any schedule for conducting such reviews.
2. *Exclusion of worker and environmental pathways.* The draft Guidance makes no attempt to take into account any exposure pathway other than food, thus disregarding both worker-associated and environmental pathways (the latter may be of especially great concern in the context of aquaculture). At the very least, failure to evaluate these pathways demands a highly conservative approach in analyzing risks and making risk management decisions.
3. *Consideration of cross-resistance and co-selection.* Cross-resistance and co-selection are not adequately addressed.
4. *Additional exposure assessment issues.* The current exposure assessment provisions operate in a way that understates the value of human drugs that are not now widely used in agriculture – even though such drugs may be particularly useful in human medicine if resistance to them is low.
5. *Need for periodic re-evaluations.* Although resistance is a dynamic function and can change substantially in a relatively short period, there is no mechanism for updating the analysis. Similarly, there is no mechanism for updating the human value of the drug – even though increased resistance to another antibiotic may, for example, quickly turn an antibiotic into the drug-of-choice. FDA should re-evaluate animal antibiotics every three to five years.
6. *Extent-of-use issues.* The key term "select groups of animals" should be much more clearly defined to differentiate use in a "select" group from use in ways that are essentially the same as flock-wide or herd-wide use.
7. *Ensuring prioritization of public health protection.* Rather than stating that all risk estimation rankings may be subject to "further refinement" based on a variety of factors, the document should make clear that refinements will be applied as needed to protect health, rather than to weaken the stringency of controls.

Additional detail on each of these points is provided below.

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## Introduction and Overview

Founded in 1967, Environmental Defense is a national, nonprofit environmental advocacy organization with more than 300,000 members throughout the United States. The technical elements of these comments were prepared principally by John Balbus, M.D., M.P.H., Director of the Environmental Health Program at Environmental Defense. Prior to joining Environmental Defense, Dr. Balbus was on the faculty of the Schools of Medicine and Public Health at The George Washington University where his work focused in part on developing methodologies for microbial risk assessment for waterborne infectious disease risks.

In addition to the points presented here, Environmental Defense concurs in the comments submitted to this docket by the Keep Antibiotics Working coalition (KAW) and by other participants in KAW.

FDA states that the draft Guidance “represents the Agency’s current thinking on a recommended approach for assessing the safety” of antibiotics and other antimicrobial drugs used in animal agriculture, with regard to their potential contribution to antibiotic resistance affecting humans. The Guidance sets forth a four-step approach for deriving a qualitative (not quantitative) risk assessment. First, a “release assessment” is conducted to assign a high, medium, or low probability that use of the antibiotic in agricultural animals will result in the development of bacterial genes coding for antibiotic resistance. Second, an “exposure assessment” is conducted to assign a high, medium, or low probability that humans will be exposed to these resistant genes via food. Third is a “consequence assessment” that ranks the importance of particular antibiotics in human medicine as high, medium, or low (FDA’s rankings are set forth in Appendix A of the document). Finally, a “risk estimation” integrates the results of the three assessments, using a grid provided by FDA that lays out all possible high/medium/low combinations of assessments and assigns an overall risk estimate of high, medium, or low (p. 21). FDA also outlines certain risk-management steps that it may adopt based on the overall risk estimate, ranging from denying the application to approving with conditions (e.g., requiring a prescription, prohibiting extra-label uses, or limiting extent-of-use in terms of duration and method of administration (individual animals vs. mass administration)).

## Substantive comments

Before turning to our concerns about the draft Guidance, there are several aspects of the draft that warrant commendation. First, Environmental Defense applauds FDA’s acknowledgement that the use of antibiotics in animal agriculture is an issue that warrants in-depth attention because of its contribution to the growing health crisis of antibiotic resistance. Second, we strongly support FDA’s statement that animal drugs can only be used if they are found to be “safe,” and that “safe” means “a reasonable certainty of no harm to human health” (Guidance, p. 2). In our view, this interpretation is not only correct, but the *only* permissible interpretation of the relevant statutory language. Third, we applaud FDA’s explicit recognition of the need to consider not only resistant pathogens, but also resistance genes (so-called “resistance determinants”) in non-pathogenic bacteria, or commensals. We strongly concur with the Guidance’s observation that “bacteria pathogenic to humans can acquire resistance traits from non-pathogenic bacteria ... by mechanisms that allow the exchange of their genetic material in the human gastrointestinal tract” (Guidance, p. 1) (an observation that also applies to the environment). At the same time, while the Guidance repeatedly refers to resistance determinants, it is not at all clear how they are to be incorporated into the evaluation process.

1. *Reviews of existing approvals.* Our chief concern is that Appendix C does not set out any timeline for reviewing antibiotics currently in use in both human medicine and animal agriculture. This task will require extensive resources, both personnel and money, to accomplish in any reasonable time frame. Indeed, as the Agency has previously noted, "The Agency's experience with contested, formal withdrawal proceedings is that the process can consume extensive periods of time and Agency resources." The Agency gave as examples the twenty-year process for withdrawing approval for nitrofurans, and the six-year process for withdrawing approval of DES.<sup>1</sup> As a result, we question whether the Guidance will prove to be effective in reducing the threat of antibiotic resistance related to the use of antibiotics in agricultural animals.

2. *Exclusion of worker and environmental pathways.* While we acknowledge that the food-borne pathways that the guidance document uses for its analysis are the most readily discerned, it is troubling that FDA makes only a passing reference to worker and environmental pathways, and fails to provide for any analysis at all of their impacts. Data on both pathways are increasingly available. Indeed, data linking routine feeding of antibiotics to colonization of workers by resistant bacteria have been available for decades.<sup>2</sup> More recently, several researchers have documented contamination of surface and ground water with antibiotics and antibiotic-resistant bacteria associated with agricultural operations associated with agricultural operations.<sup>3</sup> Such antibiotics are released from agricultural sites both intentionally, when manure is land-applied, and accidentally, when manure-storage facilities leak or overflow. Because up to 75% of the dose of an antibiotic ingested by an animal is excreted in biologically active form, manure may contain significant quantities of antibiotics, along with antibiotic-resistant bacteria<sup>4</sup> – a significant issue given that nearly two *trillion* pounds of waste is generated in the U.S. each year by cattle, poultry, and hogs.<sup>5</sup>

Environmental pathways may be of particular concern in the context of aquaculture, given that antibiotics are typically added to feed that is placed directly in water. Some of the feed is left uneaten and disperses – with the antibiotics – into the aquatic environment, along with unmetabolized antibiotics in fish feces. As a result, use of antibiotics in aquaculture can readily lead to dispersion of antibiotics in the aquatic environment. At the same time, the food pathway may be of lower concern in aquaculture than for other

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<sup>1</sup> Letter dated Feb. 28, 2001, from Stephen F. Sundlof, D.V.M., Ph.D., Director, Center for Veterinary Medicine, FDA, to Karen Forinil (sic, should be Florini), Senior Attorney, Environmental Defense, regarding FDA's second tentative response to the citizen petition that was submitted to FDA seeking withdrawal of approvals for nontherapeutic use of specific medically important antibiotics on March 9, 1999, by the Center for Science in the Public Interest et al.

<sup>2</sup> Levy S.B., G.B. FitzGerald, and A.B. Macone. 1976. Changes in intestinal flora of farm personnel after introduction of a tetracycline-supplemented feed on a farm. *New Engl. J Medicine*, 295(11): 583-588.

<sup>3</sup> Chce-Sanford J.C., R.I. Aminov, I.J. Krapac, N. Garrigues-Jeanjean, and R.I. Mackie. 2001. Occurrence and Diversity of Tetracycline Resistance Genes in Lagoons and Groundwater Underlying Two Swine Production Facilities. *Applied and Env. Microbiology*, 67(4): 1494-1502; Kolpin, D.W., E.T. Furlong, M.T. Meyers, et al. 2002. Pharmaceuticals, Hormones, and Other Organic Wastewater Contaminants in U.S. Streams, 1999-2000: A National Reconnaissance. *Env. Sci. Technol.* 36(6): 1202-1211.

<sup>4</sup> See discussion in comments of Environmental Defense, et al., on the Proposed Effluent Guidelines for Concentrated Animal Feeding Operations, EPA Docket Number OW-00-27 (submitted July 30, 2001), attached.

<sup>5</sup> See [www.scorecard.org/env-releases/aw/us.tcl](http://www.scorecard.org/env-releases/aw/us.tcl), utilizing data from the USDA 1997 Census of Agriculture and North Carolina Manual of Agricultural Chemicals, Ch. 10.

forms of animal agriculture, because finfish and crustaceans, as cold-blooded animals, are less likely to host zoonotic pathogens than livestock and poultry. Thus, the Guidance's focus on food-borne pathways is particularly ill suited for aquaculture. As a result, the Guidance should not be applied in aquaculture contexts, at least without additional emphasis on environmental pathways.

In summary, the failure to include worker and environmental pathways results in a systematic underestimation of risks associated with agricultural antibiotics and justifies conservative risk management decisions, both in aquaculture and in agriculture.

*3. Consideration of cross-resistance and co-selection.* Although the draft Guidance notes that the phenomena of cross-resistance (whereby one mechanism of resistance confers resistance to multiple antibiotics) and co-selection (whereby several genes coding for resistance mechanisms occur together, so that pressures to select one of the genes lead to the selection of multiple resistance genes for multiple antibiotics) complicate the estimation of risk of developing resistance, it does not uniformly address these issues in a clear, consistent, or health-protective manner. For example, Appendix A states that drugs for which cross-resistance has not developed would be considered of greater human importance than drugs for which cross-resistance has developed. But language in the section on release assessment implies that if a drug does not have documented cross-resistance, it will receive a lower score. This could lead to a situation in which a critically important drug, which nonetheless has some degree of cross-resistance, receives only a medium overall risk ranking because the existence of cross-resistance has lowered its medical-consequence score. Conversely, a critical drug for which cross-resistance has not yet developed might receive only a medium overall risk ranking because the lack of cross-resistance leads to only a medium risk assignment for the release assessment. In both cases, the Guidance's methodology biases towards an assignment of medium risk even for critical drugs.

In addition, the document refers to the existence of resistance determinants on multi-gene plasmids as "co-selection" in the release assessment and elsewhere refers to "cross-resistance across drug classes." This terminology should be clarified, and the terms co-selection and cross-resistance defined in the glossary. As above, Appendix A reduces the risk severity for drugs whose resistance determinants are found on multi-gene plasmids. Since the use of these drugs will impact resistance to multiple other drugs, it would be more appropriate to flag these drugs as of higher risk, not lower risk. The Guidance does provide for ranking such a drug according to the highest consequence category of the drugs for which it co-selects, but this is not sufficiently health protective, given the potential impact of multi-drug resistant bacteria.

*4. Additional exposure assessment issues.* On page 18, the "probability of human exposure to the hazardous agent" is defined to depend upon the "probability that bacteria of interest are resistant." While it is reasonable that the probability of exposure does depend on the prevalence of existing resistance, this approach creates a "catch-22" situation: from a medical perspective, the antibiotics of greatest utility are often new antibiotics, which are especially effective precisely because resistance to them is not yet widespread. An example would have been methicillin in the first years after it was approved. FDA should do all it can to prolong the effectiveness of such antibiotics. But under the current draft, newer antibiotics, because bacteria are not yet resistant to them, could be given lower scores than drugs that already had provoked widespread resistance.

Another anomaly arises for recently introduced drugs. For a drug that is not yet in use, the Guidance provides that data from the release assessment are to be substituted for data on resistance patterns (which would indicate no resistance because of lack of prior use of the drug). However, once that drug is introduced, the Guidance provides that actual data on resistance are to be used – even if the drug has been on the market for too short a period for detectable resistance to have been reported, and even if the same

data from the release assessment would continue to indicate that resistance may be expected to arise. Therefore, whichever data more strongly indicate possible resistance should be used.

5. *Need for periodic re-evaluations.* Undeniably, critical factors such as importance in human medicine and prevalence of existing resistance are dynamic, not static. As a result, periodic re-evaluation of drugs is vital. An antibiotic that may be experimental or marginal one year may become a critical lifesaver the next depending on external events. One interesting example of this phenomenon is that the current draft lists tetracyclines, including doxycycline, as being of “medium” importance – even though doxycycline became a drug of high importance in helping treat people who had potentially been exposed to anthrax during the 2001 bioterror incidents. (When Environmental Defense staff pointed out the anomaly of listing doxycycline as a “medium” ranked drug, FDA staff responded by stating that the ranking had been compiled during the summer of 2001, and had not been subsequently updated.) We therefore strongly recommend that all approvals be re-evaluated periodically, preferably every three to five years – and earlier if important new information warrants earlier review.

6. *Extent-of-use issues.* At the core of the draft Guidance is the concept of limiting risk by limiting extent and conditions of use. While this approach has much to recommend it, the current language on “select groups of animals” may create a significant loophole. Specifically, the current language states that medium use includes administration to “select groups/pens of animals” – a phrase defined in a footnote as involving “delivery of drug to a specific segregated subset of animals within a confinement facility” such as a building, house, feedlot, etc. But if “select group of animals” is broadly construed – for example to include a large number of chickens within a given poultry barn – this could end up being similar in effect to flock-wide administration. In short, FDA should add some qualifying language to the “select groups/pens of animals” to indicate that the number of animals involved is small. At the same time, we strongly support the current approach under which all flock-wide and herd-wide usage is deemed to constitute a high extent of use.

We are also concerned about consideration of extent-of-use in the release assessment (Section A.2.h.). This represents a potential loophole, an application that underestimates the actual extent of use could lead to approval of a drug, allowing unexpectedly high on-label use, or more likely, extensive off-label use. If this occurs, the actual risk would be concomitantly higher than projected. To avoid this outcome, FDA should develop a mechanism by which any drug that has medium or high risk of release or exposure is restricted to the precise extent of use described in the drug application. In particular, off-label use that would involve greater extent of use should be prohibited.

7. *Ensuring prioritization of public health protection.* We are concerned about the apparent plasticity of the risk estimation rankings. FDA states that all risk estimation rankings, particularly medium ones, may be subject to “further refinement” based on a variety of factors. While such refinements in the direction of additional stringency may be justified in order to meet FDA’s statutory obligation to protect human health, it seems highly unlikely that refinements in the direction of less stringency would ever be appropriate. FDA should clarify this in the final Guidance.

Similarly, wording of the Guidance should be changed to underscore the Agency’s primary mission to protect the public’s health. Specifically, p.15 states “If sufficient information regarding a factor is not available or has not been generated for the assessment, the most conservative significance of the particular factor may be assumed.” The word “may” here should be changed to “must,” to avoid a situation in which a lack of information leads to failure to protect public health.

In addition, the sentence "conversely, pharmacodynamics might be ranked low with regard to impact on resistance if the same drug did not enter the target animal intestinal tract at concentrations shown to have an effect on resistance development" should be changed to say that "pharmacodynamics would be ranked low if the same drug was shown to enter the target animal intestinal tract at a concentration shown *not* to have an effect on resistance development". Again, the point is to make health protective assumptions in the absence of data assuring safety – the basis of all FDA drug approvals.

## Conclusion

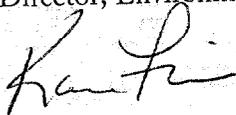
In general, the draft Guidance represents a significant step forward, but one that needs additional work to close loopholes that may otherwise eviscerate it. We urge FDA to make such changes expeditiously, as discussed above.

In addition, we urge the FDA to resist the inevitable calls for a more quantitative approach in place of the qualitative approach outlined in the guidance document. At present, we do not support additional quantification for two distinct reasons. First, the state of the science of quantitative modeling of development of antibiotic resistance is not sufficiently advanced to be used for such predictive purposes, as experience in other contexts (such as attempts to complete microbiological risk assessments for drinking-water contamination) have shown. Second, whether intended by the proponents of a quantitative approach or not, the effect would be to slow down greatly the process of review so that no effective action could be taken. The qualitative approach places less of a burden on industry (as well as FDA) to complete, as it utilizes a good deal of existing data, and it allows for a more rapid risk determination.

Thank you for this opportunity to comment.



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