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November 22, 2002

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

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

I am writing on behalf of Sierra Club's more than 700,000 members to comment on the FDA's September 6, 2002, draft document entitled "Draft Guidance for Industry: Evaluating the Safety of Antimicrobial New Animal Drugs With Regard to Their Microbiological Effects on Bacteria of Human Health Concern" (67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)).

The Sierra Club would like to begin by applauding the FDA's acknowledgment that the use of antibiotics in animal agriculture is an issue that warrants considerable attention because of its contribution to the growing health crisis of antibiotic resistance. Also, we agree with the FDA's assertion that drugs should only be used on animals if they are found to be "safe" meaning, "a reasonable certainty of no harm to human health" (Guidance, 2).

Although we are pleased with elements of the draft guidance, the Sierra Club has several concerns that will be detailed below. In addition to the points presented in this document, Sierra Club concurs with the comments submitted to this docket by other participants in the Keep Antibiotics Working coalition (KAW), including the Center for Science in the Public Interest, the Humane Society of the United States, Environmental Defense, other member organizations and KAW itself.

The areas of the guidance that could use clarification or improvement are:

- The document's lack of **timeframe for reviewing antibiotics currently in use** in animal agriculture and human medicine. This task will require substantial resources to accomplish in a reasonable time frame. Without a clear written commitment to undertaking this task in a timely manner, we question whether the guidance will prove to be effective in reducing the threat of antibiotic resistance due to the use of antibiotics in animals.

- **Periodic re-evaluation** of approved drugs is an essential element that is under-addressed in the document. The FDA should establish firm timelines and clearer guidance for periodic re-evaluation of approved drugs. The importance of drugs in human medicine is always changing over time, causing a previously marginal drug to become essential. Also, resistance is a dynamic function and can change

substantially in a relatively short period of time. For these reason, re-evaluations of approved drugs should occur every three to five years or earlier if important new information warrants earlier review.

- The ranking system set forth in the document will result in **skewed ranks due to exposure assessment** issues. Part of the reason some drugs are extremely useful in human medicine stems from the fact that there is very low resistance to them. Such drugs, despite their medical importance, might only receive a medium rank if they are not yet used in agriculture. In this way, the system would fail to preserve the utility of vital drugs. Drugs of extreme importance in medicine should automatically receive a high overall ranking removing the concerns about the use of the release and exposure assessments.

- The draft guidance does not adequately address **worker and environmental pathways**. Although food-borne pathways are a major concern, research has documented worker-related and environmental pathways for resistance development. The draft documents makes only passing reference to these issues and fails to provide for any analysis of their impacts. Not including analysis of 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. Further investigation in these other pathways should be included in the final document.

- In several instances, the language in the draft document could create **loopholes** that will undermine the effectiveness of the guidance. The document explains that medium use includes drug administration to "select groups/pens of animals." If this term is broadly construed, the result would be similar in effect to flock or herd-wide administration. The language should specify that the number of animals involved in this type of administration 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.

  Sierra Club is 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.

  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.

By incorporating these changes, the FDA's proposed guidance will become a stronger, more effective means of protecting public health. Abuse of antibiotics in factory farms threatens the usefulness of some of the most important infection fighting drugs known to modern medicine. The European Union, on the

recommendation of the World Health Organization, has banned the use of antibiotics to promote the growth of livestock animals when those drugs are also used to treat people. The Center for Disease Control has agreed with this position. It is appropriate that the United States begin to take steps to limit the use of antibiotics in agriculture when those antibiotics are also used in human medicine.

Thank you for this opportunity to comment.

Sincerely,

Ed Hopkins
Director of the Environmental Quality Program