KEEP ANTIBIOTICS WORKING
The Campaign to End Antibiotic Overuse
www.KeepAntibioticsWorking.org

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

RE: Docket No. FDA-1998-D-0038 on the Revised Draft Guidance for Industry (GFI #152): Evaluating the Safety of Antimicrobial New Animal Drugs With Regard to Their Microbiological Effects on Bacteria of Human Health Concern

Introduction

Keep Antibiotics Working (KAW)[1] is submitting these additional comments on the Revised Draft Guidance for Industry: Evaluating the Safety of Antimicrobial New Animal Drugs With Regard to Their Microbiological Effects on Bacteria of Human Health Concern (draft GFI#152). In previously submitted comments (May 18, 2023) KAW member organizations primarily focused on the drug rankings in Appendix A of the guidance. We subsequently identified additional concerns about revisions to the risk management approach included in the draft guidance. As a result, these additional comments are with respect to the management of the risk of antibiotic drugs.

Under the Federal Food, Drug, and Cosmetic Act (FDCA), drugs used in food-producing animals must be shown to be safe with respect to human health including safe with respect to antibiotic resistance. For a proposed use of a drug to be considered safe there must be "a reasonable certainty of no harm". The 2003 GFI#152, "Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern", describes the process for determining the safety of a proposed use of an antibacterial new animal drug with respect to antimicrobial resistance. The safety assessment results in an estimation of the risk to human health from the proposed use with high, medium, and low risk as potential outcomes. Clearly a finding of high or medium risk of negative human health impact does not meet the safety standard of "reasonable certainty of no harm". Instead of denying high and medium risk approvals despite not meeting the safety standard of reasonable certainty of no harm, GFI#152 allows these drugs to be approved under **specific use restrictions.** GFI#152 states that "FDA believes that antimicrobial drugs ranked as **high** risk may be approvable if, after

[1] Keep Antibiotics Working, a coalition of health, consumer, agricultural, environmental, humane, and other advocacy groups, is dedicated to eliminating the inappropriate use of antibiotics in farm animals, a significant contributor to the rise in antibiotic resistant disease.

evaluating all supporting information, FDA can conclude that there is a reasonable certainty of no harm to human health when the drug is approved under specific use restrictions". Five specific use restriction are included in the original GFI#152. One is a limit on how long a drug can be used. Under the original guidance, high or medium risk drugs should be restricted to low extent of use (Table 8, page 25) defined as no more than 21 days in groups of animals (Table 7, page 23). In the current draft, the following language has been added to the section of the guidance which defines what is considered high extent of use (Table 7, page 20):

> * *Duration of use will be revised on a case-by-case basis in light of, but not limited to, animal species, disease risk period, and animal management husbandry practices, etc.*

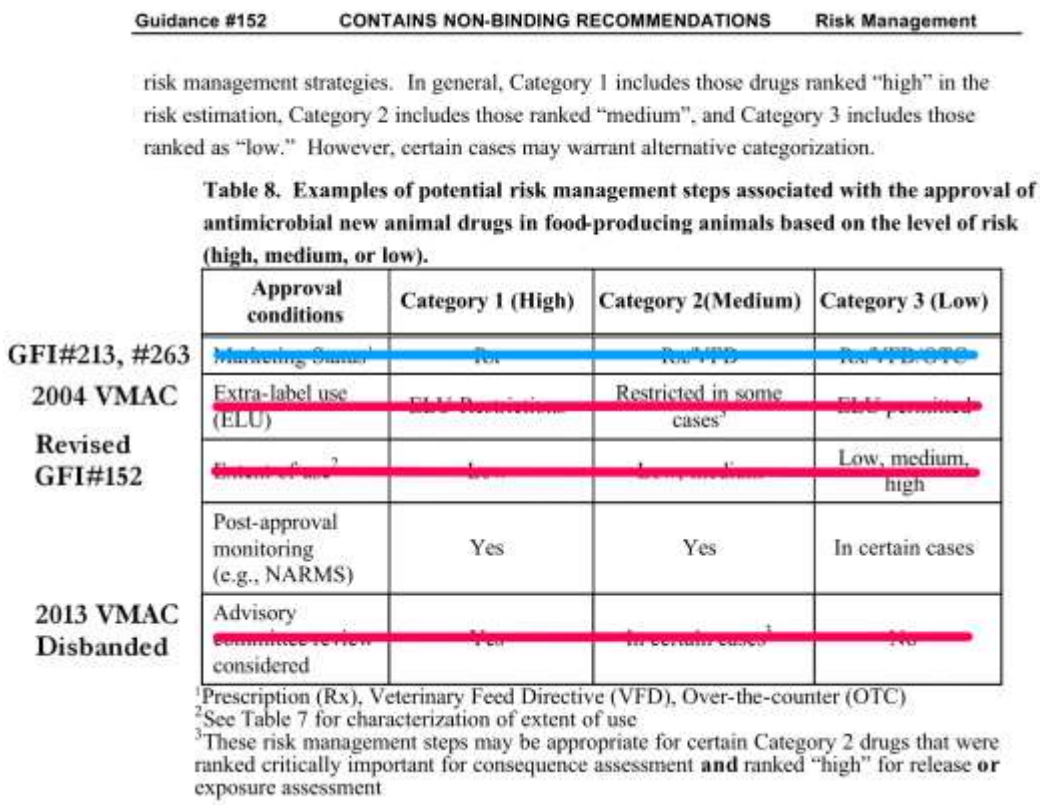
In doing this, draft GFI#152 replaces the 21-day limit which was intended to protect human health with a duration based on animal health. It is completely inappropriate for animal health needs, such as proposed in the quoted text above, to be included in a human safety review of new animal drugs. FDA regulations do not allow balancing the human safety of veterinary drugs against animal health benefits.

The irrelevance of animal health criteria to human safety decisions in the context of antibiotic resistance is extensively discussed in the 2005 Final Decision of the [FDA] Commissioner on Withdrawal of the New Drug Application for Enrofloxacin in Poultry, Docket 2000N-1571. On page 10 of the final ruling the FDA Commissioner clearly states that environmental and animal welfare benefits are not included in decisions around human safety. On page 64 the Commissioner states, "I find that the FDCA as a whole, as well as its' legislative history, makes clear that Congress did not intend to allow FDA to weigh costs or benefits associated with the use of a new animal drug in deciding whether its use has been shown to be safe for humans when used in food-producing animals". Yet the FDA is now proposing that drug sponsors to do exactly that.

The irrelevance of animal health factors to decisions on human safety criteria was also reiterated by the FDA in the recent order revoking the Approved Method for Carbadox in Medicated Swine Feed, 88 FR 76760-76770. The FDA stated that, "comments on animal health, industry economic losses, antimicrobial resistance, and human food safety" are "not relevant to whether the approved method meets our regulatory requirements and is adequate to monitor the residue of carcinogenic concern" (Page 76769).

The impact of this change in GFI#152 will be even greater because two other of the five specific use restrictions designed to make high risk drugs safe have already been eliminated by the FDA and one other has been applied outside the risk assessment framework. In addition to a restriction on the extent of use described above, the 2003 GFI#152 in Table 8 describes four other specific use restrictions appropriate for high-risk drugs: 1) restrict extra-label use, 2) review by advisory committee, 3) require a veterinarian's order, and 4) monitor post approval through the National Antimicrobial Resistance Monitoring System. Since 2003, the FDA has progressively removed most of these risk management tools.

The following diagram illustrates how the specific use restrictions in the 2003 GFI#152 have been progressively eliminated.



Guidance #152 CONTAINS NON-BINDING RECOMMENDATIONS Risk Management

risk management strategies. In general, Category 1 includes those drugs ranked "high" in the risk estimation, Category 2 includes those ranked "medium", and Category 3 includes those ranked as "low." However, certain cases may warrant alternative categorization.

Table 8. Examples of potential risk management steps associated with the approval of antimicrobial new animal drugs in food-producing animals based on the level of risk (high, medium, or low).

Approval conditions	Category 1 (High)	Category 2(Medium)	Category 3 (Low)
~~Marketing Status[1]~~	~~Rx~~	~~Rx/VFD~~	~~Rx/VFD/OTC~~
Extra-label use (ELU)	~~ELU Restrictions~~	Restricted in some cases[3]	~~ELU permitted~~
~~Extent of use[2]~~	~~Low~~	~~Low/medium~~	Low, medium, high
Post-approval monitoring (e.g., NARMS)	Yes	Yes	In certain cases
Advisory ~~committee review~~ considered	~~Yes~~	~~In certain cases[3]~~	~~No~~

GFI#213, #263
2004 VMAC
Revised GFI#152
2013 VMAC Disbanded

[1]Prescription (Rx), Veterinary Feed Directive (VFD), Over-the-counter (OTC)
[2]See Table 7 for characterization of extent of use
[3]These risk management steps may be appropriate for certain Category 2 drugs that were ranked critically important for consequence assessment **and** ranked "high" for release **or** exposure assessment

- **2004: Restricting Extra-label use removed.**
  The FDA told members of the FDA Veterinary Medicine Advisory Council (VMAC) in 2004 and 2006 that a finding of high risk was not sufficient to put in place an extra-label use restriction on a proposed use of an animal drug even after the advisory committee voted to include these restrictions. The FDA has never applied this restriction on a new animal drug in response to a review under GFI#152.

- **2013: Review by advisory council review was removed when the FDA disbanded the advisory committee.**
  The FDA disbanded VMAC in 2013. Prior to this, VMAC had voted against an approval because of resistance risk and also recommended stronger restrictions than proposed by drug sponsors and the FDA, thus improving safety.

- **2023: Veterinary oversight became a requirement for all medically important antibiotics so no longer a specific restriction for high risk drugs.**
  Guidance for Industry #263 and earlier Guidance for Industry #213 moved all medically important antibiotics used in food-producing animals under veterinary oversight.

We recommend that the FDA do the following to ensure the safety of animal drugs.

- Remove the language from draft GFI#152 that eliminates the 21-day restriction on duration of use for high and medium risk uses of animal drugs.
- Reinstate the Veterinary Medicine Advisory Committee and use it when the FDA is considering making significant changes that could impact public health.
- Clarify whether or not the FDA believes it can require an extra-label restriction at the time of approval of an animal drug and be transparent about what the inclusion of this specific use restriction means in GFI#152 in light of the clarification.