

The Comments of Food Animal Concerns Trust
On the Draft Guidance #152 Evaluating the Safety of New Animal Drugs with Regard to
Their Microbiological Effects on Bacteria of Human Concern

November 18, 2002

Comments submitted by Steven Roach, Food Safety Program Manager

Docket Number 98D-1146

General comments

Food Animal Concerns Trust (FACT) is a non-profit organization that advocates better farming practices to improve the safety of meat, milk, and eggs. FACT's food safety work focuses on researching and promoting steps that can be taken by livestock producers to reduce the risk from foodborne diseases. FACT has worked for many years now with the Food and Drug Administration (FDA) to promote appropriate regulation of antibiotic use in farm animals. FACT opposed the approval of fluoroquinolones for use in poultry, a position the FDA has subsequently accepted, when it was first proposed. FACT also worked with the agency through the participation of Richard Wood, FACT's executive director, on the FDA's Veterinary Medicine Advisory Committee. FACT brings to this discussion the perspective of consumers informed by an understanding of the best available science.

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FACT commends the Center for Veterinary Medicine (CVM) for taking this important step to help reduce the risk to American consumers from antimicrobial resistance that results from drug use in animal agriculture. FACT accepts as non-controversial that antimicrobial use in animal agriculture leads to the selection of resistant bacteria that can, through a myriad of pathways, impact human health either directly by causing illness or indirectly by transferring resistance to other pathogenic bacteria. FACT's position is consistent with that stated in a consumer advisory from the FDA dated October 2001. The advisory states that "CVM acknowledges that ... there is ample scientific data linking antimicrobial foodborne resistant infections in humans to the use of these antimicrobials in livestock and poultry (FDA, 2001)." Along with the FDA, the Centers For Disease Control and Prevention (CDC, 2002) and the World Health Organization (WHO, 2000) also accept this position.

Despite the significant evidence that antimicrobial use in animals does impact human health through the selection for resistant bacteria, there is still great uncertainty about which specific on farm practices cause the greatest harm. The FDA currently does not track even the total quantities of approved antimicrobials sold for on farm use, let alone for what indications the drugs are used, or for what species. In addition, there generally is no way to trace back from a disease causing foodborne illness to a specific farm that was the source of the bacteria. Given these gaps in the available information, the qualitative risk assessment proposed by the FDA in Draft Guidance #152: Evaluating the Safety of New Animal Drugs with Regard to Their Microbiological Effects on Bacteria

of Human Concern (Draft Guidance) is a prudent approach that aims to use what we do already know.

While FACT accepts the general approach of the FDA, we feel it is necessary to identify some areas where the Draft Guidance requires strengthening or clarification.

Specific comments

1) FACT is concerned that the Draft Guidance does not sufficiently commit the FDA to respond in a timely manner to the antimicrobials that are already approved. FACT is pleased to see that prior approvals have been moved from a footnote in the Framework Document to an appendix in the current Draft Guidance. FACT calls on the FDA to present to the public a timeline for addressing the already approved antimicrobials.

2) In a related matter, FACT is concerned that the Draft Guidance does not clearly specify how newly available information will be used to re-evaluate drugs that have already been approved under the Draft Guidance. The amount of resistance detected on farm is a moving target and is expected to rise as a drug is approved and begins to be used. Similarly, the medical importance of any given drug will change as resistance develops in human disease and as new human drugs are approved. Despite FACT's reservations about the "thresholds" approach presented by the CVM in December 1999, there was at least in that document an implicit acceptance that resistance is a moving target that is expected to increase with time. FACT calls on the FDA to include in the Draft Guidance a plan to re-evaluate all approved drugs at least every five years.

3) As noted in our general comments, the FDA's ability to appropriately address the problem of antimicrobial resistance related to drug use in animal agriculture is severely hindered by a lack of basic information. The FDA needs to collect specific enough drug use data to understand changes in resistance among pathogens in livestock populations. This data is essential to monitor the efficacy of the restrictions of use provisions described in the Draft Guidance as methods of controlling resistance. Drug use data is also important to monitor how well other resistance control measures, such as appropriate use guidelines, are working. The Office International des Epizooties has pointed out the importance of accurate use data for any antimicrobial resistance control programs (OIE, 2001). In the current Draft Guidance, the National Antimicrobial Resistance Monitoring System (NARMS) is the only post-approval monitoring mentioned. NARMS, without use data, lets us know we have a problem, but does not help us to identify how best to address the problem. FACT calls on the FDA to include drug use data as part of the post-approval monitoring of all approved antimicrobials.

4) On page 25 of the Draft Guidance, advisory committee review is proposed as one of the risk management steps. FACT believes that advisory committee review is essential for all category 1 and 2 drugs. The committee membership must be broad to insure that all stakeholders are able to provide input, include the formal participation of public health and consumer representatives. In addition, the advisory committee process should be as open as possible. FACT supports the inclusion of advisory committee review with broad committee membership and open process for all category 1 and 2 drugs.

5) FACT is concerned that the risk assessment proposed in the Draft Guidance does not place enough weight on the medical consequence section. Given that the FDA mandate is to provide reasonable certainty of no harm, FACT believes that the medical consequence section should be given greater weight than the release and exposure sections. We feel this is necessary because of the elements that the risk assessment leaves out, because of the large period of time over which a drug will be used, and because of the large populations of animals that will be treated by a given drug.

The exposure assessment in the Draft Guidance only considers the impacts of *Campylobacter* and *Salmonella* on food. This ignores the risk from other exposure pathways and from resistant commensal bacteria. There is clear evidence that the most direct pathway for resistant bacteria from animals to enter the human population is not through food, but through direct contact with animals and their manure by farm workers (Levy et al 1976, Swartz 2002). FACT is concerned that steps designed to mitigate the transmission of bacteria in food will not necessarily protect farm workers and members of their community. Additionally, the exposure assessment will also underestimate risk, because it ignores transmission through commensal bacteria (Smith et al., 2002).

Given the large populations of treated animals and the long period of time for which an antimicrobial will be used, resistance will eventually develop even for drugs ranked low for risk of release. At that time, a rapid spread through the animal population may occur. Because of the inevitability of the development of resistance once a drug is approved, and

because of the pathways that are ignored by the risk assessment procedure presented in the Draft Guidance, FACT urges the FDA to increase the weight of the human consequence section of the risk assessment. The greatest restrictions of use must be placed on the drugs most important to human medicine even if the release and exposure assessments are low.

6) While FACT agrees in principle that placing restrictions on the duration of use and on the number of animals treated may be a useful tool for limiting the development of resistance, we are concerned with the lack of accountability once a drug is on the market. The recent, September 19th, 2002 reminder to veterinarians by the CVM that extra-label use of fluoroquinolones is prohibited illustrates how difficult it is to control how drugs are used once they are approved. In this case, it is medical professionals who are flouting FDA regulations in the face of a high level of public concern about the drug class in question.

In particular, FACT is concerned that the Draft Guidance is too vague in Table 4 where it suggests that limiting use to select groups or pens of animals can be an effective tool. The Draft Guidance does not describe the size of a pen. Can a pen hold 30,000 chickens or does this mean that all poultry drugs are considered high extent-of-use? Even if this were clarified, FACT believes that the FDA has no mechanism to ensure that a whole herd is not treated as a bunch of pens.

FACT is also concerned that limitations on the duration of use may lead to practices that result in even greater resistance development. Research by Dr. Matthew at the University of Tennessee, Knoxville has shown that rotating similar drugs as an antibiotic treatment can lead to the rapid development of resistant Salmonella in swine. FACT is skeptical that there is a mechanism to ensure that a drug approved for a short duration will not be either rotated with a similar drug or used in a succession of short durations.

It has been suggested that residue testing is a mechanism to determine if drugs are used properly under the label restrictions proposed in the Draft Guidance. While residue testing can limit the risk of drug residues in food, it is an inappropriate tool to address the problem of antimicrobial resistance. Residue testing does not provide information on the duration of drug use and does not provide information on whether a whole flock has been treated inappropriately.

The most effective means to insure that extent-of-use limitations are followed is to approve drugs for delivery methods that by their nature limit use. Antimicrobials in feed or water are by their nature are designed for delivery to large numbers of animals and should be restricted to category 3 drugs that are of limited importance to human medicine. Alternatively, the FDA can develop a rigorous system of monitoring drug use on farms that is capable of determining which animals are treated, for what indications, over what duration of time.

FACT urges the FDA to clarify how it intends to monitor extent-of-use limitations and, if this is not possible, FDA should only approve category 1 and 2 drugs for use by delivery mechanisms that are not practical for treating large number of animals.

7) Given that extent-of-use limitations are the primary method of control for resistance in the Draft Guidance, it is necessary for the FDA to limit extra-label use. If this is not done, veterinarians will be able to prescribe antimicrobials in ways that increase the risk of resistance development. The Animal Drug Use Clarification Act of 1994, which describes the conditions under which extra-label drugs may be used in animal agriculture, places restrictions on uses which lead to increased risk of drug residues, but does not require that any actions be taken to limit the development of antimicrobial resistance.

FACT urges the FDA to prohibit extralabel use for all category 1 and category 2 drugs.

Conclusion

FACT generally supports the qualitative risk assessment as laid out within the Draft Guidance. FACT is concerned that the Draft Guidance does not place enough emphasis on re-evaluating approvals based on new information that becomes available after an approval has already been made. FACT strongly believes that the medical consequences section of the risk assessment should be given greater weight to meet the standard of no harm because of the large number of potential pathways of resistance transfer to humans that are ignored in the risk assessment. FACT's final reservations about the Draft Guidance center around our concern that the proposed risk management steps will not be enforceable and that the Draft Guidance describes no method to monitor compliance.

Despite these reservations, FACT sees the Draft Guidance as an important step forward in the fight to protect American consumers from harmful antimicrobial resistant bacterial infections. FACT looks forward to continuing to work with the FDA to find ways to improve the safety of food for all Americans.

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Please find the enclosed comments of Food Animal Concerns Trust for Draft Guidance 152, submitted on November 18, 2002.



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