

## Strategy for Addressing Public Health Concerns Regarding Use of Medically Important Antimicrobials in Food-Producing Animals

**Background:** The June 2010 draft guidance, *The Judicious Use of Medically Important Drugs in Food-Producing Animals* (GFI #209), recommended that steps be taken to (1) phase out the production use of medically important drugs and (2) phase in veterinary oversight of such drugs. The guidance further indicated that the agency was interested in comments as to how it could best use its regulatory authority and take non-regulatory measures to support implementation of the two key recommendations.

In developing an implementation strategy, CVM carefully considered the public comments submitted in response to draft GFI #209 and held discussions with the animal pharmaceutical industry, the animal feed industry, animal producer organizations, and veterinary organizations. CVM is encouraged by the positive response of the key stakeholders, particularly the animal pharmaceutical industry, to work cooperatively with the agency to implement the changes recommended by GFI #209.

The primary focus of the strategy at this time is on leveraging the cooperation of the pharmaceutical industry to phase in the desired changes through a voluntary process. However, although a voluntary process can provide an efficient mechanism for accomplishing these changes, we recognize that certain regulatory measures may be needed to support/encourage the voluntary process and to ensure that changes are implemented in an orderly, equitable, and timely manner.

**Core Elements of Strategy:** The proposed strategy involves the coordinated publication of three interrelated documents that are pivotal to implementing the GFI #209 recommendations. These include:

1. Publish the finalized judicious use guidance (GFI #209).
2. Publish follow-up draft guidance (GFI #213) that provides more detailed guidance to sponsors of medically important antimicrobial drugs regarding how to comply with GFI #209 recommendations. The animal pharmaceutical companies have indicated that such guidance is needed to help facilitate the implementation of FDA's recommendations.
3. Publish draft codified language providing an opportunity for the public to comment on changes being considered to streamline the veterinary feed directive (VFD) regulation, which contains the current requirements related to veterinary oversight of medicated feeds. This publication will serve to signal the agency's intentions to the industry and will facilitate the rulemaking process. The animal pharmaceutical companies have indicated that understanding FDA's intentions for updating the VFD process is critical to their decision to move forward with voluntarily complying with the GFI #209 recommendations.

### Additional Measures to Consider:

We recognize that the voluntary strategy has certain limitations in that (1) it lacks specifically defined/mandated timeframes; (2) its success is dependent on drug sponsors deciding it is in their best interest to work cooperatively with the agency; and (3) FDA collects insufficient data on drug use, as noted by GAO in their latest and not yet published report, to measure the effectiveness of the strategy. To address these limitations, several additional options are presented below for consideration.

(b) (5)



(b) (5)

**Other ongoing initiatives that support strategy include:**

- Assessment of new drug products with regard to antimicrobial resistance concerns as part of animal drug approval process (Guidance #152)
- Effort to enhance surveillance of antimicrobial resistant foodborne pathogens through NARMS program (e.g., July 2011 public meeting seeking input on NARMS improvements)
- Use of authority to prohibit extralabel use of certain antimicrobial drugs to mitigate resistance concerns (e.g., ongoing effort regarding cephalosporin drugs)
- Educational/outreach activities and international engagement (e.g., WHO, Codex, OIE)

**Proposed Timeline for Key Documents:**

<b>Elements of Strategy</b>	<b>Target Publication</b>
<i>Core documents</i>	
- Finalize GFI #209	9/30/11
- Issue draft GFI #213	9/30/11
- Publish VFD draft codified	9/30/11
<i>Additional documents</i>	
- ANPRM on drug sales/use	11/30/11
- Cephalosporin prohibition	9/11

**Coordinated rollout strategy to be developed:**

The intent is to “package” together the key documents above and publish them in a coordinated manner in conjunction with an overarching public communication strategy - conveying the message that FDA is actively implementing a comprehensive approach for addressing this important public health issue.

**FDA's Antimicrobial Resistance Strategy**  
**March 27, 2012 Discussion Bullets**

**Comments Regarding Pending FDA Documents**

***Final Guidance 209***

- Based on comments received from OMB, FDA understands that one remaining issue of concern is whether the final guidance 209 needs to include additional review of the relevant scientific literature as justification for the recommendations outlined in the document.
- In response to this concern, FDA is prepared to delay publication of the final Guidance 209 to provide time to discuss the concern further and to make appropriate changes, as necessary.
- FDA proposes that issuance of final Guidance 209 be delayed until such time as the draft Guidance 213 document is issued in final form, as these two documents are closely linked.

***Draft guidance 213***

- FDA believes it is critically important this guidance issue without further delay because:
  - Key stakeholders (including animal health/agriculture industry and consumer/public health advocacy organizations) continue to question when the agency will make available for public comment further details of its strategy for assuring the judicious use of medically important antimicrobials outlined in draft guidance 209 in June 2010.
  - As discussed below, providing further details of the agency's strategy for implementing the recommendations outlined in draft 209 is important for responding to the pending NRDC lawsuit. As noted below, issuance of guidance 213 would be most helpful in this regard if it was published by March 30.
- FDA believes that the review of guidance 213 by OMB is essentially complete and that the issues raised have been effectively addressed. However, given the recent court decision regarding one prong of the NRDC lawsuit (discussed further below), FDA is proposing that some additional clarifying language be added to the guidance. FDA believes this language may be helpful in obtaining a more favorable decision with respect to the second prong of the lawsuit. We also believe affected stakeholders and the public will find it helpful as it provides greater clarity as to the agency's intentions and, therefore, provides an opportunity for public comment on those intentions.
- FDA proposes that the following sentence that appears on page 11 of draft guidance 213 be replaced with the alternative language below:
  - Current language: *Upon issuance of final guidance, we will continue to monitor industry practices and will consider further action under the FD&C Act should adoption rates in the industry warrant it.*
  - Alternate language: *Upon issuance of final guidance, the agency will monitor the progress of its strategy for the voluntary adoption of the changes outlined, including the*

*progress of measures intended to facilitate an orderly and minimally disruptive transition. In addition, 3 years from the date of publication of the final version of this guidance, FDA intends to evaluate the rate of adoption of the proposed changes across affected products. The agency will consider further action as warranted in accordance with existing provisions of the FD&C Act for addressing matters related to the safety of approved new animal drugs.*

- In the recent decision in the NRDC lawsuit, the court expressed its view that an entirely voluntary approach to the regulation of antimicrobial animal drugs is unlawful. With regard to purely voluntary regulation, the court stated that “[t]he statute does not empower the agency to choose a different course of action in lieu of withdrawal proceedings, such as that embodied in the 2010 Draft Guidance.” Opinion at 53. The issuance of draft guidance 213 with the language proposed above may help assuage the court’s concern that FDA is failing to protect the public health in accordance with the FDCA by forecasting the possibility of appropriate regulatory action if necessary.

#### ***Veterinary Feed Directive (VFD) draft regulation***

- FDA believes it is critically important the draft VFD language be made available for public comment (in conjunction with draft guidance 213) without further delay because:
  - The primary objectives of the changes being proposed are to streamline the existing VFD regulation and reduce the burden associated with those requirements.
  - The animal pharmaceutical industry, the animal feed industry, and the animal producer and veterinary communities have all made it clear that streamlining the VFD process is pivotal to the success of the voluntary strategy outlined in guidances 209/213.
  - USDA has indicated that one of their greatest concerns is the potential impact of greater veterinary involvement on animal producers, particularly on smaller producers in remote locations. Streamlining the VFD process is a key measure for minimizing these potential impacts.
- Implementing changes to streamline the VFD process is a critical step in setting the stage for phasing in greater veterinary oversight of the use of medically important antimicrobials in animal feed (one of the key changes recommended in guidances 209/213). Therefore, it is important the draft VFD language publish concurrently with draft guidance 213 so key stakeholders and the public are more fully informed regarding FDA’s current thinking and can more effectively comment on the overall strategy.

#### **Status of Pending Lawsuit**

- In regard to the case involving *Natural Resources Defense Council, et al. v. FDA, et al.*, the following two sets of antimicrobial drugs are at issue:
  - The first set consists of penicillins and tetracyclines used in animal feed for which FDA’s Bureau of Veterinary Medicine issued two notices of opportunity for hearing (NOOH) in 1977. Last week the court ordered FDA to begin withdrawal hearings on these drugs.

Thus, unless reversed on appeal, FDA will not be able to implement a voluntary compliance policy with regard to these drugs.

- The second set consists of drugs in the 3 other classes of medically important antimicrobials used in animal feed (lincosamides, streptogramins, and macrolides) comprising approximately 85 individual applications, and is the subject of NRDC's still-pending Citizen Petition Claim.

(b) (5)



### Background

Antimicrobials have been used in modern agricultural practices for years. In addition to using these drugs for therapeutic treatment, antimicrobials are frequently added to feed on a flock or herd-wise basis for purposes such as increasing weight gain or improving feed efficiency of food-producing animals. These practices allow the use of less feed, thus reducing production costs for these animals. Although the scientific issues involving antimicrobial resistance are complex, a simple explanation is as follows: All uses of antimicrobials, whether in humans or in animals, may increase drug-resistant bacteria by killing the susceptible bacteria and allowing the bacteria resistant to the drug to multiply. When this happens in food-producing animals, the bacteria may be transferred to humans through contact with and ingestion of food from the animals. When humans are exposed to these bacteria, they can become sick. And, because the bacteria are drug-resistant, infected persons may not respond to standard treatment options, or available treatments may be less effective. As a result, people may be sick for a longer period of time than they would have been if treatment options were available.

### CVM's Recommended Approach for Addressing Concerns over Subtherapeutic Uses of Medically Important Antimicrobials in Food-Producing Animals

For several years, CVM has worked with sponsors to address concerns over the subtherapeutic uses of medically important antimicrobials in food-producing animals. These efforts have brought us closer to achieving our goals. To bring these objectives to fruition, CVM recommends a three-prong approach:

1. Finalize judicious use guidance (GFI #209);
2. Publish proposed guidance explaining how sponsors can voluntarily remove approved subtherapeutic claims from medically important antimicrobials (GFI 213);
3. Revise current Veterinary Directive Rule (VFD) to make it easier to convert current OTC status of medically important antimicrobials to VFD status – this change in status ensures appropriate veterinary oversight in the decision to use these antimicrobials in food-producing animals.

Recognizing, however, that the voluntary approach will only work if all sponsors decide it is in their best interest to work cooperatively with the agency to achieve these goals, CVM also suggests that setting out some timeframes within which we expect to see progress toward achieving these goals. These could include dates by which the sponsor: submits a letter of intent to us about how/when sponsor will remove subtherapeutic claims and change marketing status; submits supplemental application to us; notifies distributors/veterinarians about change in claims and marketing status; etc.

CVM suggests that these milestone timeframes be communicated to the sponsors through a notice in the Federal Register. This will help maintain a transparent process, and will

assure the public that we are making real-time progress toward our final goals. It will also help assure each company that FDA is treating all companies marketing similar products similarly.

In addition, we would need to think about how to determine and communicate the following:

- What should the ramifications be for missing a benchmark milestone date?
- How far should FDA go in foreshadowing regulatory action if the voluntary approach fails?
- What regulatory action should we undertake if the voluntary action fails to achieve our goals?

Available Regulatory Actions:

If the voluntary approach does not achieve our goals, there are several regulatory options available to us. They include:

(b) (5)

