The recommendations made herein are our own and are informed by our scientific training and expertise. They do not necessarily reflect the views of the Johns Hopkins University.

RE: Antimicrobial Animal Drug Sales and Distribution Reporting (FDA-2012-N-0447)

To Whom It May Concern:

Thank you for the opportunity to comment on antimicrobial sales and distribution reporting by drug sponsors to the U.S. Food and Drug Administration (FDA). The Johns Hopkins Center for a Livable Future (CLF) is an academic research and education center based at the Bloomberg School of Public Health that investigates the interconnections among food systems, public health, and the environment. CLF has conducted and supported numerous studies of antimicrobial use in food animal production and antimicrobial resistance. We believe it is imperative that antimicrobials be used responsibly in food animal production to help slow the development of antimicrobial resistance, which has emerged as a major threat to both human and animal health.

A critical component of assuring responsible antimicrobial use is the ongoing collection and dissemination of comprehensive data on the administration of these drugs to food animals. These data provide public health, medical, and veterinary stakeholders the information they need to investigate the development and spread of antimicrobial resistance and to make informed decisions regarding antimicrobial use in human and non-human patients. This information also enables the formulation and evaluation of evidence-based public policy. Specifically, antimicrobial new animal drug sales data will allow FDA to evaluate the success of Guidance for Industry (GFI) #209 and GFI #213 and identify additional policies as necessary. For these reasons, we offer the following recommendations for FDA to improve monitoring of antimicrobial sales and use in food animal production:

1. FDA should require sponsors of antimicrobial new animal drugs to report additional information on antimicrobial sales under Part 512(l)(1) of the Federal Food, Drug, and Cosmetic Act (21 USC §360b(l)(1)), including antimicrobial new animal drug sales by state.

In a comment on ADUFA submitted in December 2011, CLF recommended that FDA ask Congress to improve the geographic resolution of antimicrobial sales data by requiring drug sponsors to report
these data by state. We still believe that FDA should ask Congress to require such reporting under ADUFA. It may be possible to collect these data under Part 512(l)(1) as well, however. Because geographic patterns of antimicrobial resistance may reflect geographic patterns of antimicrobial use in food animals, information on antimicrobial sales by state (or even by county or zip code) may support a determination concerning the safety of an approved antimicrobial new animal drug and subsequent proceedings to withdraw that approval. These data also may assist veterinary clinicians in making more informed decisions regarding antimicrobial use by revealing regional trends in use over time.

Part 512(l)(1) reads in relevant part, “In the case of any new animal drug...the applicant [drug sponsor] shall establish and maintain such records, and make such reports to the Secretary, of...data or information, received or otherwise obtained by such applicant with respect to such drug, or with respect to animal feeds bearing or containing such drug, as the Secretary may by general regulation...prescribe on the basis of a finding that such records and reports are necessary in order to enable the Secretary to determine, or facilitate a determination, whether there is or may be ground for” withdrawing approval of the new animal drug in question.

FDA therefore has the authority to establish recordkeeping and reporting requirements for sponsors of any new animal drug if those requirements are necessary to determine, or facilitate a determination, that an approved new animal drug is “unsafe” or “not shown to be safe” under Part 512(e) and must therefore be withdrawn. We believe that currently available evidence supports withdrawal of approvals to use antimicrobial new animal drugs for growth promotion and disease prevention. Nevertheless, FDA may determine that comparison of geographic patterns of antimicrobial use and resistance can provide additional evidence to support withdrawal proceedings, where appropriate, and as a result, the agency should collect this antimicrobial sales information via Part 512(l)(1).

2. FDA should include all data collected under Section 105 of the Animal Drug User Fee Act (21 USC §360b(l)(3)) (ADUFA) that may be released under the statute in the annual summary, especially breakdowns of sales of each antimicrobial class by dosage form.

ADUFA requires drug sponsors to report sales of antimicrobial new animal drugs to FDA and directs the agency to release annual summaries of these data to the public. A large fraction of antimicrobial sales data collected by the agency (i.e., the quantity of each antimicrobial active ingredient or antimicrobial class sold by container size, strength, and dosage form, including the target animals, indications, and production classes for which each dosage form is approved) has not been released to the public. This means that public health researchers lack basic information about antimicrobial sales and use, limiting our ability to investigate associations between antimicrobial use and patterns of resistance and to recommend and evaluate evidence-based policies aimed at slowing the development and spread of antimicrobial-resistance determinants.

For example, it should be public knowledge what proportions of products in different antimicrobial classes are formulated for use in feed and drinking water, which could permit inferences to be made about how products in these classes are used, as particular indications require antimicrobials to be formulated in specific ways (i.e., herd- or flock-wide administration of antimicrobials for growth promotion or feed efficiency typically requires administration in medicated feed or drinking water).
The administration of antimicrobials in feed poses a higher risk of selection for antimicrobial resistance than use by injection, as FDA has acknowledged, making data on dosage form especially important.

CLF has made recommendations on ADUFA to FDA at one public meeting and in three private meetings. We initially asked that all data on sales of antimicrobial new animal drugs in classes with three or more distinct sponsors be released, as the statute does not appear to prohibit their release. FDA responded that specific categories of new animal drugs in each class (e.g., penicillins formulated for use in feed) may only include the sales of fewer than three distinct sponsors and that the agency considers data on sales of these categories exempt from release as well. We do not agree with this reasoning. The statute reads, “no class with fewer than 3 distinct sponsors of approved applications shall be independently reported” (emphasis added); it does not refer to categories within classes with three or more distinct sponsors.

If FDA believes that it may not release such data, it should still release, by antimicrobial class, all data that may be reported within these supposed constraints. For example, if there are three or more distinct sponsors of penicillins formulated for use in drinking water, but fewer than three distinct sponsors of penicillins formulated for use in feed or by injection, then the quantity of penicillins formulated for use in drinking water should be released in the public summary. It is the role of public health researchers, not just FDA, to determine the utility of these data. FDA should therefore maximize the availability of ADUFA data within any statutory constraints it perceives.

3. FDA should recommend to Congress, as part of the ADUFA reauthorization process, that ADUFA be amended so that annual public summaries include data on all antimicrobial classes, regardless of the number of distinct sponsors of new animal drugs in those classes.

ADUFA prohibits the release of data on sales of antimicrobial classes with fewer than three distinct sponsors. Multiple antimicrobial classes—including the critically important fluoroquinolones and streptogramins—are currently covered by this requirement. As discussed above, FDA also believes this requirement proscribes the release of additional data on antimicrobial classes with three or more distinct sponsors. This requirement is therefore the primary obstacle to public health and veterinary researchers who need such data to conduct scientific analyses evaluating human and animal health outcomes of antimicrobial use.


FDA and drug sponsors may believe that antimicrobial new animal drug sales data of each drug sponsor constitute confidential business information and are therefore exempt from disclosure even in the absence of the explicit requirement contained in ADUFA. If so, FDA should provide specific examples of competitive harm that would be incurred by drug sponsors if ADUFA data were released in full. It seems highly unlikely that releasing these data would harm the competitive position of drug sponsors. In any case, the public interest in knowing more about antimicrobial use in food animal production and the attendant development and spread of antimicrobial resistance far outweighs the narrow interests of drug sponsors. FDA should recommend that Congress remove this requirement when ADUFA is reauthorized. The agency should also work to ensure that all antimicrobial sales data collected under ADUFA are publicly released.

4. FDA should use the veterinary feed directive (VFD) regulation (21 CFR §558.6) to collect detailed data on the administration of antimicrobial new animal drugs in medicated feed.

The sales data collected under ADUFA are important but imperfect surrogates for antimicrobial use. Antimicrobial use data must be collected further along the supply chain, ideally at the individual farms where these drugs are consumed. Under 21 CFR §558.6, veterinary feed directive (VFD) drugs may not be administered in animal feed except in accordance with a VFD issued by a licensed veterinarian. Each VFD contains information relevant to monitoring antimicrobial use and correlating use with antimicrobial resistance. Because the veterinarian issuing the VFD must provide copies to the client and feed distributor, because each party must keep the VFD on file for at least two years, and because FDA already has the authority to inspect and copy these records, it should be possible for the agency to systematically collect, aggregate, and publicly release detailed data on antimicrobial use in medicated feed. As current over-the-counter (OTC) antimicrobials are transitioned to VFD status under Guidance for Industry (GFI) #213, it will become possible to monitor all in-feed antimicrobial use in this way. These data would be superior to ADUFA sales data for understanding patterns of antimicrobial use and resistance.

FDA should also expand the VFD recordkeeping requirements to collect information of relevance to antimicrobial resistance. For example, the agency should require veterinarians to specify the number of animals, animals species, animal production class (by weight or age), and disease indication. Epidemiologic studies provide evidence of a strong association of human carriage of methicillin-resistant Staphylococcus aureus (MRSA) with exposure to breeding pigs (i.e., sows and very young pigs) relative to associations observed with exposure to older pigs (i.e., farrow-to-finish pigs). The collection of these data would provide important information for characterizing risk of colonization or infection in frequently exposed populations (e.g. veterinarians, farm workers).


5. FDA should integrate antimicrobial sales and use data from multiple sources throughout the new animal drug supply chain to verify the accuracy of reported data and assure that antimicrobial new animal drugs are used legally.

The collection of antimicrobial sales data under ADUFA and the collection of antimicrobial use data under the VFD regulation, combined with records maintained by feed mills under 21 CFR §225.202, should be used to verify the accuracy of data collected from each source. For example, when antimicrobial new animal drugs formulated for in-feed use are transitioned from OTC to VFD status under GFI #213, the quantity of drugs distributed for in-feed use by feed mills should correspond to the quantity ordered by area veterinarians, as reflected by records maintained under the feed mill and VFD regulations. Discrepancies between data collected from different sources may signal inaccurate reporting and, in some cases, illegal use of antimicrobial new animal drugs. FDA could then initiate an investigation to verify the accuracy of the reported data and assure legal use of these drugs.

It has been well demonstrated that the use of antimicrobials in food animals for growth promotion and disease prevention is an important contributor to antimicrobial resistance in bacterial pathogens of public and animal health importance. The collection of additional data on antimicrobial sales and use could help evaluate the actions taken by FDA to address these uses and suggest additional policies to effectively tackle this public health challenge. Additionally, better data could support further research on this topic and inform clinical decision-making by physicians and veterinarians who are increasingly faced with patients afflicted by antimicrobial-resistant infections. We are willing to work with the agency to implement our recommendations. Please contact us with questions about this comment.

Sincerely,

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