

Richard A. Carnevale, VMD
Vice-President, Scientific, Regulatory, and International Affairs

October 19, 2012

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

Re: Docket No. FDA-2012-N-0447; Antimicrobial Animal Drug Sales and Distribution Reporting; Advance notice of proposed rulemaking

The ANIMAL HEALTH INSTITUTE (“AHI”) submits these comments to Docket No. FDA-2012-N-0447. AHI is the national trade association representing manufacturers of animal health products -- the pharmaceuticals, biological products and feed additives used in modern food production, and the medicines that keep livestock and pets healthy. AHI member companies represent the majority of companies producing antibiotics used in animal production and thus have a keen interest in the request for comments on data collection.

AHI is in a unique position to comment on this ANPR in that its member companies can actually provide insight into whether or not it is feasible to comply with the request for additional sales data. Importantly, the request may affect the commercial interests of AHI member companies and no other stakeholders. Through its counterpart associations in Europe and elsewhere, AHI has direct experience with a variety of data collection and summarization approaches. AHI recognizes the importance of the public health and food safety issue with regard to food borne antimicrobial resistance. The specific objective of potentially correlating antimicrobial sales data to national antimicrobial resistance monitoring programs, as proposed in the request for comments, needs further detailed consideration. AHI appreciates the opportunity to contribute its views.

Section II A. Sales and Distribution Data by Species

Any “usage” reporting or estimation system should be designed around goals and objectives that the data will be applied to. These goals and objectives should be clearly stated before a reporting or estimation system is designed and should be capable of answering these questions in a manner that is effective and accurate. Therefore, FDA should clearly articulate the scientific basis and circumstances for an expanded sales data report; it is not acceptable to justify the requirement because it will support NARMS in some undefined manner. Additionally, the subsequent inferential methodology relating national sales data to NARMS data should be communicated in order to determine if the sampling methodology and analysis is sufficient. Without this transparency, the value of attempting to provide this additional desired data for valid scientific inquiry remains uncertain.

AHI recommends that policy and decision-makers at FDA and other agencies read the information published in a special issue of Preventive Veterinary Medicine on the topic of antibiotic sales and use data (see attachment). The Alliance for the Prudent Use of Antibiotics sponsored the stakeholder meetings that resulted in these publications. Of note are two overview articles that provide information on the sales and distribution channels for veterinary medicinal products in the US and methodological evaluations for obtaining data (DeVincent and Viola, 2006; Viola and DeVincent, 2006). The complexity of attempting to track product beyond the immediate animal health company customer is discussed.

AHI undertook an internal survey of its member companies to evaluate the feasibility of providing “additional sales and distribution information including, for antimicrobial animal drug products that are approved and labeled for more than one food-producing animal species, an estimate of the amount of each active antimicrobial ingredient sold or distributed for use in each approved food-producing animal species”. Specifically, companies were asked to comment on “how sponsors can both practically and accurately provide separate sales and distribution information for each species”. The short answer is that sponsors can neither provide such additional sales estimate breakouts nor distribution data, nor assure the accuracy, even if the Agency makes it a requirement.

As mentioned before, the two review articles by DeVincent and Viola, 2006 and Viola and DeVincent, 2006, provide detailed insight into the complexity of the sales, distribution and end-user network. Manufacturers sell antimicrobial drug products to distributors, veterinarians, or producer buying groups and, in some instances, directly to producers. The antimicrobial products may be used directly by these buyers or they may be sold to a variety of different distributors or intermediaries which complicates the distribution channel and makes it impossible to ascertain the amount sold for use in a particular animal species or the ultimate end use of products labeled for multiple species. Thus, once the product has been sold to the primary customer, there is no practical means for a sponsor to further track a multi-label product with respect to subsequent distribution for use in a particular animal species or its actual intended use in a food-producing animal.

For example, assume Product “X” is an antimicrobial labeled for both cattle and swine. The manufacturer sells a large quantity of Product “X” to a cattle-only practice that further distributes a portion or all of Product “X” to a buying group. The buying group then distributes Product “X” to a swine-only practice. The manufacturer would assume and report that the entire quantity was used for cattle when in fact at least a portion of it was used for swine. Due to these complicated distribution networks, it is impossible for the manufacturer to accurately report the sales and distribution of antimicrobial products per food-producing species.

Moreover, due to perceived differences in corporate systems and business practices between companies, the likelihood of providing an accurate assessment of sales at the species level is unknown. The possibility of providing estimates of use, as illustrated in the example above, are thus likely to be highly variable even between companies. This situation is similar to most other multi-use products sold in the US where more detailed sales is not available the

further into the distribution network the product moves. For example, a gasoline refiner would sell various grades of gasoline and even diesel products to various distributors, with those products then sold at filling stations, but there is no means to determine what products were sold for which type of vehicle. The manufacturer knows the total amount of each product sold to which distributor but cannot obtain more detailed data.

The Section 105 sales data provided by sponsors cannot be further broken out into sales per species with any known degree of accuracy, and estimates of such break-outs are likely to vary significantly from company to company. Moreover, the ability for each company to determine how much of a multi-labeled product that was sold to a specific animal species group cannot be matched to its ultimate use.

Given the above, AHI member company sponsors would not be able to provide additional sales and distribution data by species because it is impractical to obtain, and its accuracy cannot be assured.

Section II B. FDA’s Annual Summary Report

While the inclusion of Section 105 in ADUFA was driven by a desire for antibiotic sales data, Congress also recognized the importance of confidentiality. While directing FDA to publicly release summaries of the data, Congress also directed that classes of compounds with less than three distinct sponsors should not be independently reported and included a general directive to protect both national security and confidential business information (CBI).

Although FDA’s Summary Reports in 2010 and 2011 adhere to these principles, subsequent communication and release of additional information in a political context skirts the “three or more distinct sponsors” rule. The ability to protect CBI is essential to commercial interests and competitiveness. As the trade association representing member companies, AHI is extremely concerned about the agency’s ability to protect CBI in the face of political influence and pressure for additional disclosure of submitted data. AHI believes the sales data summaries released by FDA under Section 105 of the Animal Drug User Fee Act (ADUFA) have already been misused in this manner to overstate the risk to human health from the use of antibiotics in animal agriculture. This misuse has come despite the caveats and warnings FDA issued both in the April 19, 2011 letter to Congresswoman Louise Slaughter and the subsequent Caution Document posted on the CVM website:

<http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm261160.htm>)

FDA/CVM has requested more detailed data from new animal drug sponsors on sales per species. The small and decreasing number of sponsors makes it difficult to adhere to the “three or more distinct sponsors” rule with national data reporting, and increased granularity will only make it more difficult to prevent disclosure of confidential business information. While industry structure is constantly evolving, largely due to consolidation, protection of confidential business information will likely necessitate larger groupings of antibiotic classes and animal species in order to prevent disclosure when data is summarized and reported.

It is crucial that any new data requirements include clear and effective methods for protecting confidential business information. FDA needs to include guidelines for its own organization for protecting CBI of animal health companies and observe those guidelines despite outside pressure to release additional information. The guidelines need to be continually assessed in light of industry changes.

The request for input “on how best to compile and present this summary information” leads to the possibility of other approaches. The House of Representatives Committee Report 110-804 makes it clear that Congress expects FDA to use the submitted sales data in its ongoing efforts to assess the risk of antibiotic resistance. Thus, one major change that FDA should consider is to eliminate the reporting of ionophores and other compounds not used in human medicine (i.e. not medically important). Since these compounds clearly do not contribute to the human burden of antibiotic resistance, they are irrelevant to the purpose of assessing risk. Indeed, Denmark does not consider ionophores as antibiotics and does not include the sales of ionophores in its annual DANMAP reports. As mentioned above, inclusion of these products in total sales has led to misrepresentation by certain organizations and individuals. International comparisons would be facilitated by the elimination of ionophores from U.S. reporting.

In the absence of eliminating these compounds from the annual reports, FDA should make a clear distinction between quantities of compounds sold for use in animals that have human medical uses and quantities sold for use in animals with no or unimportant human medical uses. CVM provided such a distinction in response to a Congressional inquiry so we see no reason such a distinction cannot be made in the annual public report, provided such a distinction does not disclose confidential business information. In general, while we appreciate the caveats CVM has issued in regard to the Section 105 reports, we believe the Agency can provide additional context and analysis in future reports.

Along these lines, FDA should consider reporting quantities sold based on the three levels of importance (important, highly important and critically important) in Guidance for Industry #152, Appendix A. Such a change would at least provide further context to the level of risk assigned by Guidance #152 to the various antibiotic classes used in human medicine. However, attention to CBI would need to be assured. An example of this approach is contained in the publication by Apley *et al.*, 2011. The simple publication of sales numbers with no context does not advance the Agency’s public health mission nor does it assist in the assessment of the risk of antibiotic resistance. Since it is clearly obvious that the aggregate amount of antibiotic sales in animals cannot be correlated with the risk of food borne antibiotic resistant bacteria to human health, AHI urges the Agency to advance an alternative method outlined in more detail below.

Section II C. Alternative Methods for Obtaining Antimicrobial Use Data

There is substantial discussion on alternative methods to derive estimates of antibiotic use in the Preventive Veterinary Medicine articles mentioned previously. A recent approach by

Apley *et al.* (2011) attempted to calculate the total amount of antibiotic sold (in kilograms of active ingredient) by means of an estimation process based on various farm-level input parameters. End-user survey responses on the intention of use of the administered antibiotics was variable and not always in conformance to label indications. Certainly such an estimation approach from field-based calculations back toward national amounts of antibiotic sold may be appropriate for an academic exercise, but it offers no advantage to sponsors or the Agency since the “back calculation” was designed to arrive at the sales number which is already provided. It would seem that this estimation approach would be very difficult to pursue with any degree of accuracy or veracity by either a drug sponsor or the Agency.

A variety of European approaches to estimate use of antibiotics have been taken. However, the application of these approaches by the Agency would seem problematic within the mandate of Section 105. Some of these were reviewed in the Preventive Veterinary Medicine papers. Newer approaches taken in Europe propose various calculations such as DDDs, ADDs, mg/kg per biomass and other creative descriptions (Grave *et al.*, 2010; Pardon *et al.*, 2012). None of these approaches have been successfully matched to AMR data from national surveillance programs, and some questions have arisen regarding national sales data comparisons to on-farm use estimates (Bondt *et al.*, 2012). It is clear that in spite of international harmonization guidelines provided by the OIE, there remain significant challenges to the issue of obtaining and applying antibiotic sales data to anything more than local situations. (http://www.oie.int/index.php?id=169&L=0&htmfile=chapitre_1.6.8.htm) Within the mandate of Section 105, the use of alternative methods of sales data analysis as used in other countries, do not seem feasible. Should those methods be of interest to the Agency, a special expert panel, perhaps analogous to that of the APUA stakeholder panel, should be convened for input.

It is concerning that the ANPR states that the “sales and distribution information that is currently being collected from antimicrobial new animal drug sponsors in accordance with ADUFA 105 is important in supporting efforts such as the National Antimicrobial Resistance Monitoring System (NARMS)...” since there is no methodology provided for associating the two programs. This was never the original intention of the antibiotic sales data collection program, thus to imply that it was so intended underscores the reality of the need for a workable protocol going forward. A perspective on the epidemiological challenges of linking national level sales data to other national level data like NARMS was published 6 years ago, so the need for a clear protocol or method prior to engaging in data collection or estimation should have been clear, yet apparently went unrecognized (Singer, 2006).

In fact, attempts to utilize national level sales data in an effort to estimate annual antimicrobial usage among food animals has led to falsely inflated perceptions of the human risk of contracting antimicrobial resistant food borne bacteria from meat commodities. GAO has since portrayed this current methodology of sales data collection as not sufficient to analyze trends in antibiotic resistance (Federal Register/Vol. 77, No. 145/Friday, July 27, 2012).

Even though farm level or end-user antibiotic use data (e.g. feedlots, finishing barns, etc.) would provide results that are most representative of current use practices, it appears to be the FDA's desire to further utilize national level sales data to break out the amounts sold for use in each food animal species in the belief that it would better correlate antimicrobial resistance data with antimicrobial product exposure, as recommended by GAO. Multiple antimicrobial products (especially injectable and feed formulations) are currently labeled for more than one food animal species (e.g. cattle and swine). Although the total amount of active antimicrobial ingredients sold into commercial channels is accurately provided to FDA/CVM by individual sponsors in Section 105 compliance submissions, an attempt to further categorize sales into specific species is a highly imprecise exercise as described previously. Additionally, because these data are still far removed from the end-user, this envisioned data application (like the current sales reporting methodology) is simply not representative of actual usage (DeVincent and Viola, Viola and DeVincent 2006). Therefore, the end result of applying even species-specific sales data to inferential analyses will likely increase the probability of false assumptions and conclusions as described above.

The NARMS retail data is viewed by many as a definitive indicator of the potential risk of contracting antimicrobial-resistant bacteria from meat commodities. However, these reported estimates of the prevalence of antimicrobial-resistant bacteria on meat are hampered by very small numbers and limited geographic representation. Therefore, they may suggest a falsely elevated risk, given the small probability of the resistant bacteria surviving the cooking process, the probability of a consumer actually getting sick, the probability of going to the doctor to seek care, and the probability of being treated with an antibiotic to which the respective pathogen is resistant. Matching NARMS data to sales data at a national level because of an association, but not a correlation, led to the Agency decision to remove enrofloxacin approval in 2005. Since that time, the prevalence of ciprofloxacin-resistant campylobacter on chicken meat has increased despite a lack of enrofloxacin exposure in poultry (NARMS Final Report, 2010). Thus, AHI is very concerned that without a strong scientific protocol to clearly outline how national sales data can be correlated to NARMS data, additional products will be placed at risk of Agency action or label restrictions. Failure to provide such a protocol has the potential to lead to erroneous associations between antibiotic exposure and antimicrobial resistance that will neither protect public health or food safety and will likely jeopardize animal health and welfare. AHI supports additional research investigations generated by NARMS data.

The measurement of antibiotic sales or use as an indication of the effectiveness of the voluntary actions to be taken on antibiotic products cannot be considered as an indicator of "success" of Guidance for Industry #209 or #213. As mentioned before, and in more detail below, there is currently no method in place that will accurately link sales or use data to antimicrobial resistant food borne bacteria prevalence within the NARMS program. Indeed, antibiotics used therapeutically must be evaluated within the context of US animal populations, disease prevalence and other factors.

If the agency determines that additional sales data would be useful, it should articulate the specific application of additional sales data in the context of NARMS data (within the new

NARMS approach) and provide protocols necessary for collecting, summarizing, analyzing and linking such national level data prior to pursuing a regulation to require sponsors to provide more detailed breakout sales data.

AHI believes FDA/CVM would better achieve its mission if it were to focus efforts on collecting and applying farm level antibiotic use information that could improve antibiotic use decisions by veterinarians. This approach was recommended by AHI in the Preventive Veterinary Medicine perspectives paper (Carnevale and Shryock, 2006) and endorsed by other stakeholders in their comments. In order to accomplish this objective FDA/CVM must work in conjunction with USDA. As noted previously, USDA, not FDA, has authority for on-farm access. There is precedent for this approach:

- The USDA ARS, under the direction of Dr. Paula Fedorka-Cray, initiated such a program – Collaboration on Animal Health and Food Safety Epidemiology (CAHFSE). The feasibility of the approach was mentioned in the GAO report “ANTIBIOTIC RESISTANCE Agencies Have Made Limited Progress Addressing Antibiotic Use in Animals” (September, 2011, <http://www.gao.gov/products/GAO-11-801>), noting that cost considerations, confidentiality and collaboration issues were overcome to generate useful data. Unfortunately the program funding was discontinued.

- The NARMS Strategic Plan 2012-2016 outlines goals and objectives that are worthwhile considering:
(<http://www.fda.gov/downloads/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/NationalAntimicrobialResistanceMonitoringSystem/UCM236283.pdf>)

It’s important to note that Strategic Goal 1 is to develop a sampling strategy that is more representative of food animal production and consumption and more applicable to trend analysis. Within Goal 1, *Objective 1.3*: Conduct pilot studies to collect animal drug use and resistance data on-farm to assess the feasibility of a pre-harvest sampling approach for NARMS in dairy and feedlot cattle, poultry, and swine. This on-farm approach is consistent with the AHI recommendation made in the 2006 Preventive Veterinary Medicine perspective publication (Carnevale and Shryock, 2006). It is also consistent with the now defunct USDA ARS CAHFSE program. It’s important to note that in the Strategic Plan, the use of Section 105 sales data as important to match to the data in NARMS is not even mentioned. Instead, the ability to integrate food animal production site-specific intentions of use of an antibiotic (indication, dose, route and duration) with clinical outcome and microbiological data were recognized as fundamental to determine contemporary antibiotic use practices and resulting effects. In this way, for multiple production sites, it might be possible to construct improved antibiotic use recommendations. Thus, the contradiction between the scientific approach of FDA NARMS and FDA/CVM’s request to animal drug sponsors for additional sales data, at the recommendation of GAO, needs to be reconciled.

- The USDA NAHMS reports provide another means for FDA/CVM to collaborate to obtain additional information about on-farm antibiotic use. The end-user surveys that NAHMS conducts provide the best information available as to what is actually done on-farm. This approach may accommodate the Section II C. request for Alternative Methods for Obtaining Antimicrobial Use Data
- Pardon *et al.* (2012) make the statement, “Since not all drugs delivered to a farm are used and because treatment practices are not always in compliance with the manufacturers’ instructions, the most accurate information on drug use is obtained by monitoring the end-users. Monitoring practices at the end-user level can provide essential information on what aspects of responsible antimicrobial use are in need of specific training within a certain sector”.

AHI urges FDA/CVM, in conjunction with USDA, to focus efforts and resources on the collection of farm-level data, e.g. as in the NARMS Strategic Plan, that can be assessed in the context of other surveillance and monitoring data available from NAHMS. Efforts like this, rather than the collection of additional national sales data, will yield information that can actually help producers and veterinarians make better decisions about antibiotic use. Actions taken on a farm level are the only practical way to proceed to achieve the desired result regarding the development and spread of antimicrobial resistant bacteria in food producing animals.

Moving toward an antibiotic usage study that accurately reflects animal production practices, as part of the USDA-FDA efforts should be done systematically and with the input of appropriate stakeholders. The National Chicken Council, National Turkey Federation, National Pork Producers Council and National Cattlemen’s Beef Association, are producer organizations that have previously conducted antibiotic use surveys among their constituents. They remain possible collaborators for obtaining on-farm antibiotic use data.

Data reporting formats are tied to data collections and context information, thus it is important for FDA/CVM to consider what information is available in addition to the sales data currently provided in order to analyze and report it in a meaningful and useful manner. As recommended previously, on-farm use data collection as part of a research program within USDA and FDA and other stakeholders would yield the more valuable information than will the sales and use estimates that the ANPR requests.

Conclusions and Recommendations:

- Because so many antimicrobial products have multiple species labeling, AHI member company sponsors would be unable to provide additional sales and distribution data by species because it is impractical to obtain and its accuracy cannot be assured.
- It is crucial that any new data requirements include clear and effective methods for protecting confidential business information. FDA needs to include guidelines for its

own organization for protecting CBI of animal health companies and observe those guidelines despite outside pressure to release additional information.

- International comparisons would be facilitated by the elimination of ionophores from U.S. reporting.
- FDA should make a clear distinction between quantities of compounds sold for use in animals that have human medical uses and quantities sold for use in animals with no or unimportant human medical uses.
- FDA should consider reporting quantities sold based on the three levels of importance (important, highly important and critically important) in Guidance for Industry #152, Appendix A.
- If the agency determines that additional sales data would be useful, it should articulate the specific application of additional sales data in the context of NARMS data (within the new NARMS approach) and provide protocols necessary for collecting, summarizing, analyzing and linking such national level data prior to pursuing a regulation to require sponsors to provide more detailed breakout sales data.

AHI believes that dealing with the antibiotic sales/use issue via regulation within the context of legislation is not conducive to addressing the public health and food safety concerns of antimicrobial resistant food borne bacteria. New regulation will not provide any clarity to this issue, as has been made clear in these comments and will only lead to more confusion. A more appropriate mechanism to achieve the objective may be via guidance and/or interagency agreements as NARMS and NAHMS are included.

Thank you in advance for your consideration of these comments. Should you have any questions, please do not hesitate to contact AHI at (202) 637-2440.

Sincerely,



Richard A. Carnevale, VMD

References

Apley, M.D. *et al.* 2011. Use Estimates of In-Feed Antimicrobials in Swine Production in the United States. *Foodborne Pathogens and Disease* 9(3):1-8.

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Grave, K, *et al.* 2010. Comparison of the sales of veterinary antibacterial agents between 10 European countries. *J. Antimicrob. Chemother.* 65:2037-2040.

Pardon, *et al.* 2012. Prospective study on quantitative and qualitative antimicrobial and anti-inflammatory drug use in white veal calves, *J. Antimicrob. Chemother.* doi:10.1093/jac/dkr570.

Attachment:

It is important for FDA/CVM to recognize the complexity the animal health market and distribution channel system operative in the US. The Alliance for the Prudent Use of Antibiotics sponsored an invited participant workshop in 2002 with the discussion published in Preventive Veterinary Medicine in 2006. The Table of Contents is provided below for easy reference; individual articles may be accessed via:

http://www.sciencedirect.com/science?_ob=ArticleListURL&_method=list&_ArticleListID=244217&_sort=r&_st=13&_view=c&_acct=C000024438&_version=1&_urlVersion=0&_userid=499562&md5=d680a02a888cc92f49dd85bd48833716&searchtype=a

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