FDA Center for Veterinary Medicine

FDA's Proposed Method for Adjusting Data on Antimicrobials Sold or Distributed for Use in Food-Producing Animals, Using a Biomass Denominator

Objective

FDA is proposing a method for using a biomass denominator to adjust annual data on the amount of approved or conditionally approved antimicrobial new animal drugs sold or distributed for use in food-producing animals in the United States. A biomass denominator is defined as the population of a given livestock species in the U.S. multiplied by the average weight of that species.

The proposed method will provide estimates of annual antimicrobial drug sales adjusted for the size of the animal population (the animal biomass) potentially being treated with those drugs. The adjusted estimates will provide insight into broad shifts in the amount of antimicrobials sold for use in food-producing animals and give the agency a more nuanced view of why sales increase or decrease over time in a manner that is specific to U.S. animal production.

The agency is seeking comments from the public on the proposed methodology.

Background

Other countries/regions have used a biomass denominator to adjust antimicrobial sales data for use in food-producing animals, which are applicable to their own characteristics of animal production. This section provides brief examples of some of these international efforts.

European Union (EU) and the European Economic Area (EEA)

As part of the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project, the European Medicines Agency (EMA) has published reports using a biomass denominator to adjust antimicrobial sales data from various EU member states and EEA countries. ESVAC's method uses livestock population data and standard "average weights at treatment" to establish a population correction unit (PCU) for each participating country. Average weight at treatment is defined by EMA as the theoretical weight at the time most likely for treatment.[1,2] The PCU is then used as the denominator to adjust annual sales data for that country. The PCU is defined as a technical unit of measure where 1 PCU = 1 kilogram of biomass of different categories of livestock and slaughtered animals.[3]

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[1] European Medicines Agency, Trends in the sales of veterinary antimicrobial agents in nine European countries; Reporting period: 2005-2009, http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/09/WC500112309.pdf

[2] M.H.M.M. Montforts 1999. Environmental risk assessment for veterinary medicinal products. Part 1. Other than GMO-containing and immunological products. First update. http://rivm.openrepository.com/rivm/bitstream/10029/10110/1/601300001.pdf

[3] European Medicines Agency, Trends in the sales of veterinary antimicrobial agents in nine European countries; Reporting period: 2005-2009, http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/09/WC500112309.pdf

First, the number of animals in a defined animal category from a particular country is multiplied by ESVAC's standard average weight at treatment for that animal category. The resulting value is the estimated animal biomass for the specific animal category. Second, the estimated animal biomass values for all animal categories are added together to determine the country's annual PCU. The country's total antimicrobial sales and sales by antimicrobial drug class are converted into a "mg/PCU" value, where the numerator is milligrams (mg) of the drug sold in that country and the denominator is always the country's annual PCU, regardless of the drug being represented. ESVAC's annual reports provide the mg/PCU values and percent change over time for each country. EMA uses the mg/PCU values to estimate temporal trends in the amount of antimicrobials sold for food-producing animals within individual countries and across countries.[4] Additionally, several EU member states have incorporated variations on the mg/PCU calculation and biomass denominator into their country-specific reports.[5,6]

Canada

Canada's Public Health Agency has incorporated ESVAC's method into its 2015 Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS) annual report. The report indicates that CIPARS is currently working with Canadian stakeholders to calculate and use a biomass denominator that more accurately reflects animal weights at treatment and animal categories in Canada.[7]

World Organisation for Animal Health (OIE)

The World Organisation for Animal Health (OIE) is in the process of developing a database on the amount of antimicrobials sold for use in food-producing animals worldwide. An *ad hoc* group within OIE is discussing how to present this information and how to potentially use a biomass denominator to adjust the data across OIE member countries. The *ad hoc* group has taken note of the ESVAC method and is discussing alternatives that may be appropriate for data collected from all OIE member countries.[8, 9]

Adapting Existing Models to Reflect Sales and Distribution of Antimicrobials for Use in Food-Producing Animals in the U.S.

The previous examples reflect international efforts to adjust antimicrobial sales data within individual countries and across countries relative to each country's animal population. ESVAC's method to calculate the biomass denominator for EU member states and EEA countries may

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[4] European Medicines Agency, Trends in the sales of veterinary antimicrobial agents in nine European countries; Reporting period: 2005-2009, http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/09/WC500112309.pdf

[5] Veterinary Medicines Directorate, *Veterinary Antimicrobial Resistance and Sales Surveillance 2014*; https://www.gov.uk/government/publications/veterinary-antimicrobial-resistance-and-sales-surveillance-2014

[6] French agency for food, environmental and occupational health & safety, *Sales survey of Veterinary Medicinal Products containing Antimicrobials in France – 2014: Annual Report*, https://www.anses.fr/en/system/files/ANMV-Ra-Antibiotiques2014EN.pdf

[7] Public Health Agency of Canada, *Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS) Annual Report*, http://www.phac-aspc.gc.ca/cipars-picra/2012/index-eng.php

[8] World Health Organisation for Animal Health, Report of the Meeting of the OIE Scientific Commission for Animal Diseases: Paris, 9-13 February 2015, http://www.oie.int/fileadmin/Home/eng/Internationa_Standard_Setting/docs/pdf/SCAD/A_SCAD_Feb2015.pdf

[9] World Health Organisation for Animal Health, Report of the Meeting of the OIE Scientific Commission for Animal Diseases: Paris, 7-11 September 2015, http://www.oie.int/fileadmin/Home/eng/Internationa_Standard_Setting/docs/pdf/SCAD/A_SCAD_Sept2015.pdf

have significant limitations for the U.S. with respect to key components of the denominator. Regarding animal weight, food-producing animals in the U.S. are generally larger at similar points in the production cycle than in Europe, and therefore, the standard average weights at treatment may be different. Since a large number of food animals are produced in the U.S., even a small variation in the average weight assigned to certain animal categories (i.e., broiler chickens or beef cattle), when multiplied by the number of animals, could have a significant impact on a biomass denominator.[10]

Also, management practices and the number and type of antimicrobials approved for use in food-producing animals differ between the U.S. and Europe. Additionally, all drug classes are not approved for all animal species and production classes. For the reasons described in this section, a denominator that includes all species and production class categories may not be appropriate for all antimicrobial drug classes in the U.S.

A U.S. Specific Biomass Denominator

After considering various methods used by other countries to apply a biomass denominator to adjust antimicrobial sales data in food-producing animals, the agency is proposing a U.S.-specific method that takes into account domestic animal populations and weights. FDA is proposing a method to calculate a biomass denominator that best fits the circumstances of animal production in the U.S. A biomass denominator that is specific to domestic livestock populations and animal drug approvals will:

- Allow for the most appropriate representation of antimicrobial sales data relative to food animal biomass in the U.S.;
- Adjust antimicrobial sales data to allow for additional trend analysis beyond the analysis of antimicrobial sales data alone; and
- Allow FDA to better interpret trends in antimicrobial sales data relative to U.S. livestock populations.

Key Elements of Proposed Method

The goal of the proposed method is to provide adjusted estimates that represent, reasonably accurately, trends in antimicrobial sales relative to the animal biomass of the livestock population in which the antimicrobials are being used. FDA thinks that these sales data should be assessed at the drug class level and the proposed method will allow the agency to do so.

[10] Food and Agriculture Organization of the United Nations, Statistics Division (FAOSTAT), Available from http://www.fao.org/faostat/en/#data/QL

The key elements of the proposed method are:

1) Antimicrobial sales and distribution data reported annually to FDA;

2) Annually reported animal populations in the U.S.;

3) Annually reported animal weights in the U.S.;

4) Animal drug approvals in the U.S.; and

5) Limitations on the use of certain antimicrobial drugs and/or drug classes in the U.S.

FDA intends to calculate a milligram per kilogram (mg/kg) value for at least the antimicrobial drug classes that are important in human medicine[11] (e.g., aminoglycosides, cephalosporins, fluoroquinolones, lincosamides, macrolides, penicillins, sulfonamides, and tetracyclines). In the proposed calculation, the numerator is the amount—expressed in mg—of a particular drug class sold for use in a given food-producing species, based on antimicrobial sales and distribution data reported annually by animal drug sponsors to FDA.[12] The denominator represents the animal biomass—expressed in kg—of the given species.

FDA proposes to calculate four biomass denominators, one for each of the four major food-producing species—cattle, swine, chickens, and turkeys. The biomass denominator for each species is referred to as a target animal biomass (TAB). The proposed method uses the TAB to adjust antimicrobial sales data to the drug class level according to species:

> mg/TAB = (the sum of all sales of an antimicrobial drug class, in mg, for a given target animal species)/(estimated number of the given target animal species * estimated average weight, in kg, of this species)

FDA is currently considering how best to make biomass-adjusted antimicrobial sales data available to the public.

Numerator Parameters in Detail

Sales and Distribution Data by Antimicrobial Drug Class

In the mg/TAB value, the numerator represents the sum of all antimicrobial sales and distribution data for a single species across an antimicrobial drug class. Each year, as required by statute, FDA publishes an Annual Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals (Annual Summary Report).[13] Based on statutory requirements to report summary data in a way that protects both national security and confidential business information, FDA is limited in how the agency can summarize and report data.[14] Currently,

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[11] Antimicrobial drugs and their associated classes listed in Appendix A of FDA's Guidance for Industry #152, available at http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052519.pdf.

[12] Final Rule: Antimicrobial Animal Drug Sales and Distribution Reporting, 81 FR 29129, https://www.federalregister.gov/articles/2016/05/11/2016-11082/antimicrobial-animal-drug-sales-and-distribution-reporting

[13] FDA's 2015 *Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals,* https://www.fda.gov/downloads/ForIndustry/UserFees/AnimalDrugUserFeeActADUFA/UCM534243.pdf

[14] Section 512(l)(3)(E) of the Food Drug & Cosmetic Act [21 U.S.C. 360b(l)(3)(E)]

FDA reports antimicrobial sales and distribution data in total kilograms of active ingredient by antimicrobial drug class and importance in human medicine. FDA further breaks down the data by route of administration (feed, water, injection, intramammary, etc.) and marketing status (over-the-counter, prescription, or veterinary feed directive), where these data can be publicly reported.

Antimicrobial sales and distribution data represent the amount of product entering the distribution chain in 1 calendar year, but not necessarily the total amount of product purchased by the end user to administer to animals in the same year. Additionally, while sales and distribution data provide important information about the amount of product entering distribution channels, these data do not necessarily correspond to the amount of antimicrobial drug that is actually being used in animals.

Estimates of Antimicrobial Sales and Distribution by Species

Many antimicrobial products have approved indications for multiple species. This leads to challenges, as there has been no accurate way to assign an amount of drug to a single species or know the amount distributed relative to the size of an animal population. However, on May 11, 2016, FDA issued a final rule on antimicrobial drug sales and distribution reporting. [15] The regulation (title 21, Code of Federal Regulations, section 514.87) includes the requirement for providing a species-specific estimate of sales for each antimicrobial product as a percentage of total sales. As a result, beginning in 2017 animal drug sponsors are required to provide species-specific estimates of the percentage of each antimicrobial active ingredient sold for use in the four major food-producing species. The estimates will allow FDA to separate out antimicrobial drug sales for these four major food-producing species. The sales-by-species reports will also include an "other species/unknown" category that covers approved indications for minor food-producing species, such as sheep, goats, and fish, and companion animals. Extralabel uses involving unapproved species will also fall into this category.

After animal drug sponsors begin reporting the required estimated sales-per-species data and FDA has reviewed those data, the agency will consider the feasibility of using more detailed numerators to calculate mg/TAB values. Examples include a numerator that reflects the amount of an antimicrobial drug administered in feed to a certain major food-producing species, or the amount of an antimicrobial drug that was authorized for use in a given species through a veterinary feed directive.

Denominator Parameters in Detail

In the mg/TAB value, the denominator represents the biomass for a single livestock species, which is calculated by multiplying the population by the average weight. Because the U.S. Department of Agriculture (USDA) collects data that best represent domestic livestock populations, FDA proposes using USDA's existing databases to estimate annual livestock numbers for the biomass denominator.

[15] Final Rule: Antimicrobial Animal Drug Sales and Distribution Reporting, 81 FR 29129, https://www.federalregister.gov/articles/2016/05/11/2016-11082/antimicrobial-animal-drug-sales-and-distribution-reporting

Estimates of Livestock Numbers

The proposed method relies on two USDA sources for livestock population data—the National Agricultural Statistics Service (NASS) and the Economic Research Service (ERS). FDA proposes to incorporate the following information to estimate the number of animals in a particular U.S. livestock population:

- Annual totals of slaughtered animals, based on NASS reports. For some species, the reports break down the numbers into subcategories; for example, the number of cattle slaughtered annually is broken down into calves and vealers, dairy cattle, and additional classes of beef cattle where available;[16]

- Inventory of livestock at a single timepoint, based on NASS calculations done in either January or December of the calendar year, depending on the species; and

- Annual totals of animals imported into or exported from the U.S., based on ERS reports on the international trade of livestock and meat.[17]

Although the above numbers represent a significant proportion of a U.S. livestock population, they may not include 100% of the animals within that population potentially treated with antimicrobials sold in the U.S.

Estimates of Livestock Weights

Many international methods use an estimated "weight at treatment" for an average-sized animal to calculate a biomass denominator.[18] These "weight at treatment" estimates generally do not vary by drug class or route of administration, each of which may have varying ages at treatment, and are not re-evaluated annually. Additionally, reliable data on use practices for the major food-producing species is not available, therefore calculating an "average weight at treatment" for each drug class and species combination for antimicrobials used in the U.S. would introduce too much uncertainty. Rather than weights at treatment, FDA's proposed method uses annual weights. By re-evaluating livestock weights on an annual basis, the agency will be able to capture shifts in animal demographics that may result from changing management practices, changing antimicrobial use practices, or additional factors, such as infectious disease outbreaks and changes in disease incidence rates.

As with the population data, the proposed method relies mainly on data from USDA's NASS and ERS to calculate annual average weights of livestock populations. FDA proposes to incorporate the following information to estimate the annual average weight of a particular U.S. livestock population:

[16] USDA NASS Statistics by Subject, https://www.nass.usda.gov/Statistics_by_Subject/?sector=ANIMALS%20&%20PRODUCTS

[17] USDA ERS Livestock & Meat International Trade Data, https://www.ers.usda.gov/data-products/livestock-and-meat-international-trade-data/

[18] European Medicines Agency, Trends in the sales of veterinary antimicrobial agents in nine European countries; Reporting period: 2005-2009, http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/09/WC500112309.pdf

- Average weight at slaughter, based on NASS reports. For some species, the reports break down the numbers into subcategories.

- Weights for animals imported to or exported from the U.S. will be based on weight categorizations used in USDA ERS reports on livestock and meat international trade.

- For livestock kept longer than 1 calendar year (e.g., dairy cattle, sows, and beef cattle), FDA will calculate annual average weights using information from NASS annual reports or USDA's periodic species-specific reports (e.g., reports by USDA's National Animal Health Monitoring System). In cases where annual average weights are unavailable from USDA sources, FDA may calculate average weights based on academic resources or publications[19,20] or on information contained in approved new animal drug applications or abbreviated new animal drug applications.

Similar to methods used by other countries, FDA's proposed method does not incorporate antimicrobial use practices, so animals' actual exposure to antimicrobials is not being assessed. Rather than assessing antimicrobial exposure using this method, the agency wants to best capture annual changes in antimicrobial sales and distribution relative to the animal population. FDA is aware that, in many cases, weights at slaughter aren't the same as weights at treatment; however, the agency thinks that the proposed average weight estimates are appropriate for capturing these annual changes, allowing for useful trend analysis.

Additional breakdown of species categories

FDA can only report summary antimicrobial sales and distribution data by class to protect confidential business information. However, animal drug sponsors report sales data to FDA at an individual product level. Therefore, for certain antimicrobial drug classes, FDA might calculate the target animal biomass for each species and a specific production class listed on the approved label.

For example, several products in the cephalosporin drug class are approved for use in chickens and turkeys; however, these uses are restricted to use in day-old chicks and day-old poults. The biomass denominator for chickens and turkeys for cephalosporins would not need to account for full-size broiler chickens or slaughter-weight turkeys. Instead, it would only need to account for population and average weight estimates of day-old chicks and poults. Therefore, in this example, FDA proposes applying only hatchery data gathered from USDA's inventory of livestock[21] rather than broiler or turkey data from USDA's annual slaughter totals.

[19] Iowa State University Extension and Outreach, http://www.extension.iastate.edu/AGDm/livestock/html/b1-30.html
[20] Purdue University, Purdue College of Agriculture, Food Animal Education Network, http://www.ansc.purdue.edu/faen/index.html
[21] USDA NASS Statistics by Subject, https://www.nass.usda.gov/Statistics_by_Subject/?sector=ANIMALS%20&%20PRODUCTS

Explanation of Imported and Exported Animals

It is assumed that if an animal is treated with antimicrobials prior to being imported to the U.S. or after it is exported, that treatment would be with antimicrobials not accounted for in the domestic sales and distribution data of the numerator. Therefore, similar to the ESVAC method,[22] for animals imported for slaughter/fattening the biomass of the animals at the time they are imported is subtracted from the total biomass denominator. Animals exported from the U.S. are added to the denominator at the weight category in which they are exported. Table 1 provides an example of how the biomass denominator would be calculated for swine.

Table 1: Example TAB Calculation for Swine

Production Class	Weight	Population
Slaughtered Pigs	W_1	P_1
Imported Slaughter Pigs	W_2	P_2
Exported Slaughter Pigs	W_3	P_3
Imported Fattening Pigs	W_4	P_4
Exported Fattening Pigs	W_5	P_5
Live Sow	W_6	P_6

$TAB_{SWINE} = (W_1 P_1 - W_2 P_2 + W_3 P_3 - W_4 P_4 + W_5 P_5 + W_6 P_6)$ (kg)

Applying the mg/TAB formula

As a result of the May 2016 final rule on antimicrobial drug sales and distribution reporting, animal drug sponsors must report to FDA separate sales and distribution estimates for cattle, swine, chickens, and turkeys. Calendar year 2016 will be the first year that such species-specific sales data will be estimated and reported.

To calculate the mg/TAB values for cattle, swine, chickens, and turkeys, FDA will incorporate the estimated sales-by-species data reported by animal drug sponsors, and the livestock population and weight estimates based on the sources referenced in the above section.

> mg/TAB = (the sum of all sales of an antimicrobial drug class, in mg, for a given target animal species)/(estimated number of the given target animal species * estimated average weight, in kg, of this species) [see Figure 1]

[22] European Medicines Agency, Trends in the sales of veterinary antimicrobial agents in nine European countries; Reporting period: 2005-2009, http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/09/WC500112309.pdf

Figure 1: Example of how FDA will apply the mg/TAB formula at the antimicrobial drug class level

mg/TAB value for Cattle = $\frac{\text{All sales of an antimicrobial drug class for use in cattle (mg)}}{(\text{Population} \times \text{Annual average weight})_{\text{cattle}}\ (\text{kg})}$

mg/TAB value for Swine = $\frac{\text{All sales of an antimicrobial drug class for use in swine (mg)}}{(\text{Population} \times \text{Annual average weight})_{\text{swine}}\ (\text{kg})}$

mg/TAB value for Chickens = $\frac{\text{All sales of an antimicrobial drug class for use in chickens (mg)}}{(\text{Population} \times \text{Annual average weight})_{\text{chickens}}\ (\text{kg})}$

mg/TAB value for Turkeys = $\frac{\text{All sales of an antimicrobial drug class for use in turkeys (mg)}}{(\text{Population} \times \text{Annual average weight})_{\text{turkeys}}\ (\text{kg})}$

FDA cannot calculate a mg/TAB value for the "other species/unknown" category, as it includes sales for minor food-producing species and companion animals, as well as any extralabel use, and finding appropriate values for estimating associated animal population numbers and weights for a wide variety of animals is not feasible for all categories.

FDA recognizes that some antimicrobials are sold for use in specific production classes within a larger species group (e.g., intramammary antimicrobial products for dairy cattle only). The biomass of these subsets of animals can differ drastically from the biomass of the larger species group. The proposed method can account for these biomass differences by providing the option to separate out antimicrobial sales data for specific production classes (see Figure 2).

For a numerator that includes only intramammary products in a specific drug class, the TAB denominator would only include the population and weight of dairy cattle.

Figure 2: Example of how FDA will apply the mg/TAB formula to subsets of animals

Within one drug class, separate out intramammary products for use in dairy cattle only

$$\frac{\text{All sales of an antimicrobial drug class for intramammary uses in dairy cattle (mg)}}{(\text{Population} \times \text{Annual average weight})_{\text{dairy cattle}}\ (\text{kg})}$$

Example of How FDA might Apply the mg/TAB Formula and Present the Adjusted Data

The following simulation is an example of how FDA might use the mg/TAB formula to adjust antimicrobial sales and distribution data and how the agency might present such data. The simulation is based on hypothetical sales data for antimicrobial "Drug Class X" containing antimicrobial drug products "Drug A," "Drug B," "Drug C," and "Drug D."

Total sales and distribution data for each drug were randomly generated for calendar years 2011 through 2014 and do not represent real sales of an actual drug class. The species-specific estimates were based on a random simulation program that approximated annual sales-by-species trends. The four hypothetical drugs have different animal drug sponsors, so the reported data would meet statutory requirements for reporting relating to the confidentiality of sales and distribution data.[23] There were no restrictions or limitations on the use of the drugs in any species, so no limitations on the TAB were needed. The simulated data are presented below in Table 2.

[23] Final Rule: Antimicrobial Animal Drug Sales and Distribution Reporting, 81 FR 29129, https://www.federalregister.gov/articles/2016/05/11/2016-11082/antimicrobial-animal-drug-sales-and-distribution-reporting

Table 2: Total Sales and Estimated Sales by Species for Drug Class X

Metric	2011	2012	2013	2014
Total Sales (kg)	101,706	108,210	108,185	112,699

Sales for use in Cattle

Metric	2011	2012	2013	2014
Sales (kg)	40,911	41,582	41,082	50,454
TAB (Target Animal Biomass in kg)	41,250,365,528	40,424,448,583	40,055,097,236	39,304,550,148
mg/TAB[24]	0.992	1.029	1.026	1.284

Sales for use in Swine

Metric	2011	2012	2013	2014
Sales (kg)	26,884	23,019	24,808	27,569
TAB (Target Animal Biomass in kg)	14,694,911,375	14,999,866,125	14,336,397,250	14,804,101,106
mg/TAB	1.829	1.535	1.730	1.862

Sales for use in Chickens

Metric	2011	2012	2013	2014
Sales (kg)	21,874	29,858	28,942	21,822
TAB (Target Animal Biomass in kg)	22,836,466,210	22,726,914,100	23,265,153,640	23,573,320,640
mg/TAB	0.958	1.314	1.244	0.926

Sales for use in Turkeys

Metric	2011	2012	2013	2014
Sales (kg)	8,737	9,821	10,334	9,957
TAB (Target Animal Biomass in kg)	3,295,367,400	3,385,097,760	3,291,557,500	3,260,582,260
mg/TAB	2.651	2.901	3.140	3.054

Sales for use in "All Other/Unknown" Species

Metric	2011	2012	2013	2014
Sales (kg)	3,300	3,930	3,019	2,897
% of total	3.24%	3.63%	2.79%	2.57%

FDA proposes using percent change as the primary metric to analyze and compare annual trends in antimicrobials sales and distribution data for food-producing animals. Figures 3 through 6 below depict percent change in simulated sales by species (amount expressed in kg of drug sold) and percent change in simulated sales by species adjusted using a biomass denominator. The formula to calculate percent change is: [(sales for year 2 – sales for year 1)/sales for year 1] * 100. The figures represent FDA's proposed format for assessing trends within a single species and for showing the effect of adjusting the data relative to animal biomass.

[24] Multiply sales in kg by 1,000,000 to convert to sales in mg: sales in kg * 1,000,000 = sales in mg. The sales in mg value is then used in the mg/TAB calculation.

Figure 3: Annual Percent Change in Simulated Sales for Cattle (kg) and in Simulated Sales Adjusted using the Biomass Denominator (mg/TAB) for Cattle

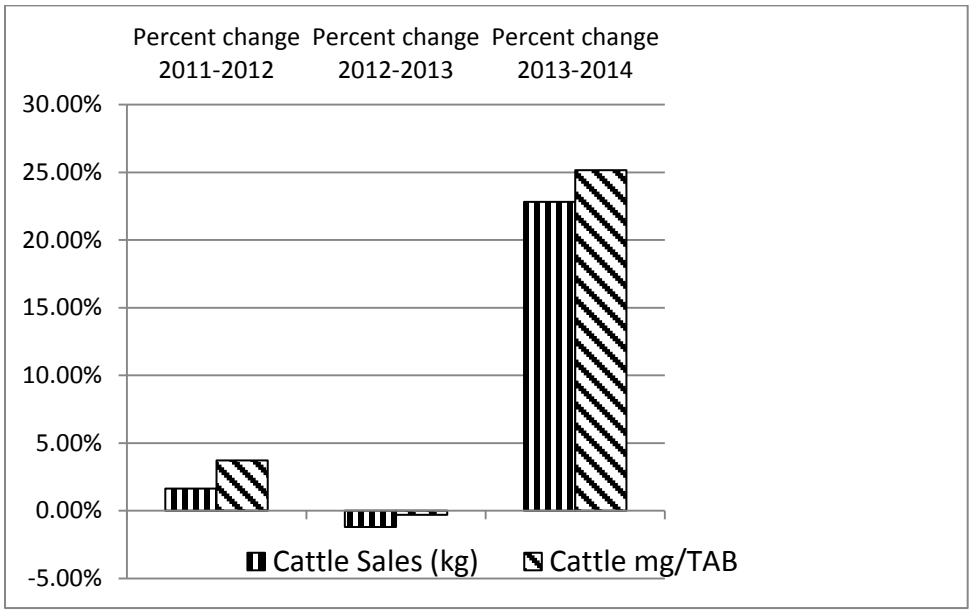


Figure 4: Annual Percent Change in Simulated Sales for Swine (kg) and in Simulated Sales Adjusted using the Biomass Denominator (mg/TAB) for Swine

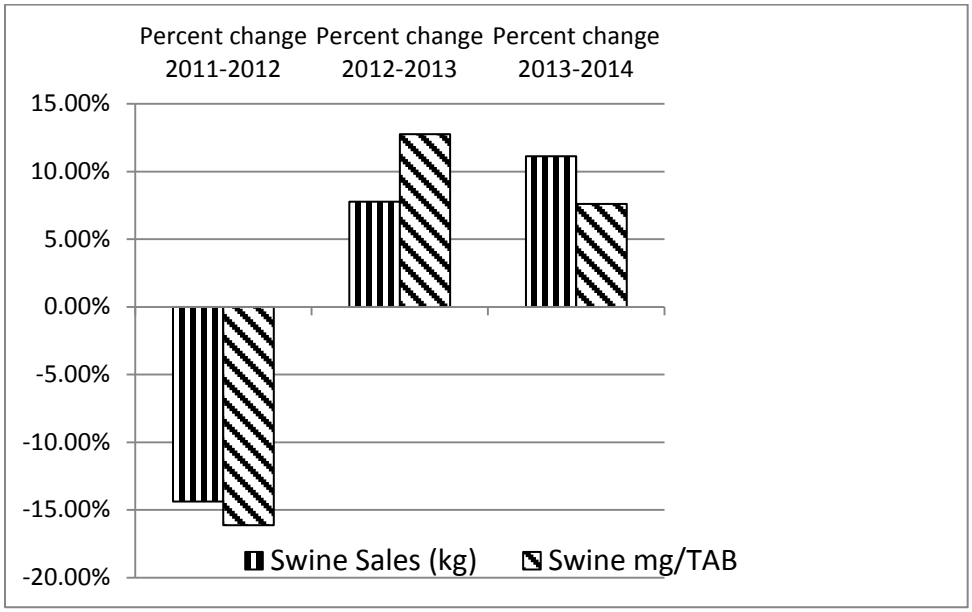


Figure 5: Annual Percent Change in Simulated Sales for Chickens (kg) and in Simulated Sales Adjusted using the Biomass Denominator (mg/TAB) for Chickens

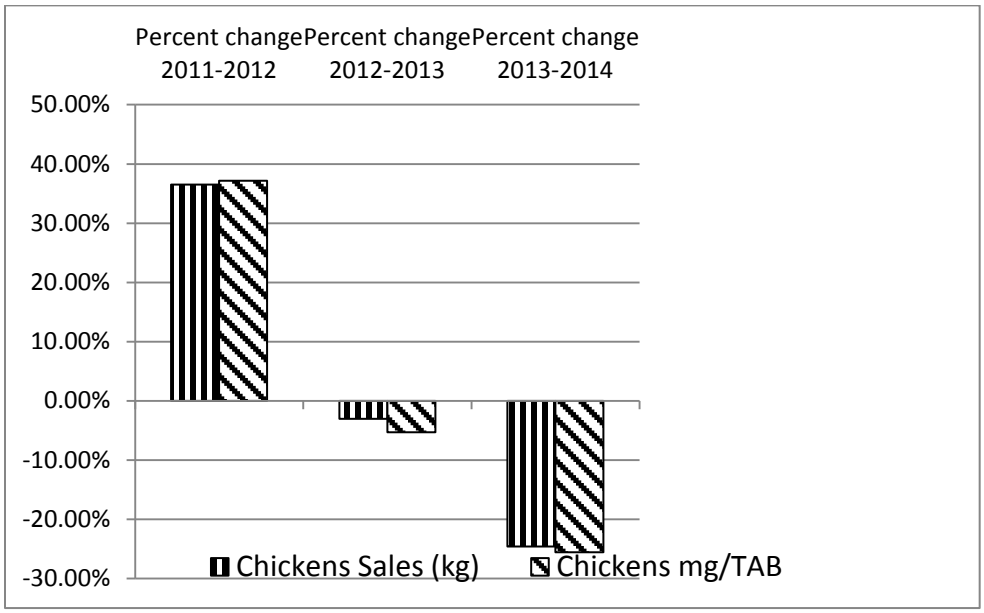
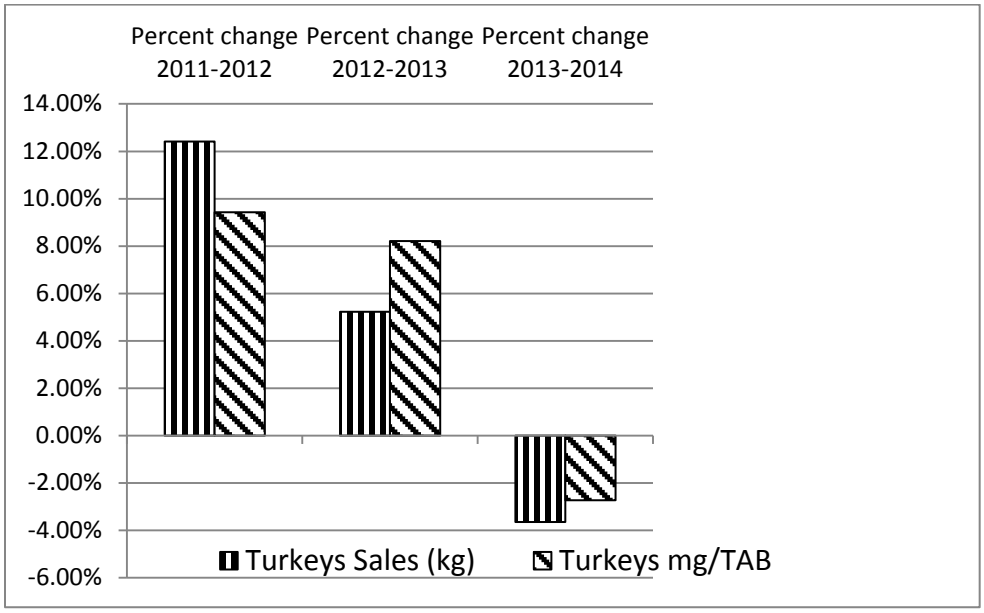


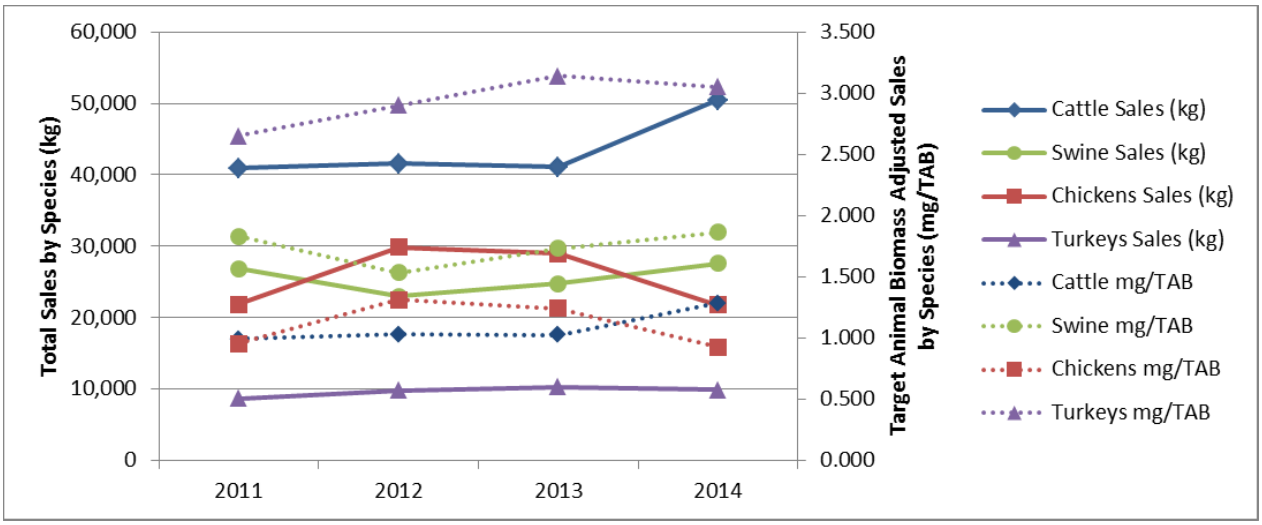
Figure 6: Annual Percent Change in Simulated Sales for Turkeys (kg) and in Simulated Sales Adjusted using the Biomass Denominator (mg/TAB) for Turkeys



As previously noted, the proposed method would provide a way for FDA to adjust species-specific antimicrobial sales data relative to the size of the animal population in which the drugs will potentially be used. In Figure 7 below, the adjusted sales-by-species data (expressed in kg of an antimicrobial drug class sold for use in cattle, swine, chickens, and turkeys) are plotted in solid lines using the left Y-axis values. The sales-by-species data adjusted using a biomass

denominator (mg/TAB) are plotted in dotted lines using the right Y-axis values. As shown in Figure 7, before sales are adjusted with the biomass denominator it appears that from 2011 through 2014, the majority of Drug Class X were sold to cattle, followed by chickens, then swine, and finally turkeys. However, when the biomass denominator is used to adjust the simulated sales-by-species data, the estimated sales of Drug Class X for use in turkeys are much higher than the estimated sales for use in the other three species. This figure demonstrates the value of adjusting the sales-by-species data. Sales data alone may be misleading because they do not account for the size of the animal population nor for the weight of the animal. Additionally, this figure shows how adjusted sales may represent a more accurate reflection of year-to-year changes in sales data. Trends appear to be similar for adjusted vs non-adjusted data from cattle, swine, and chickens. However, a slight variation is observed among turkeys.

Figure 7: Simulated Sales by Species (kg) vs Simulated Sales by Species Adjusted using a Biomass Denominator (mg/TAB)



Benefits of Biomass-Adjusted Data

FDA's proposed method to use a biomass denominator to adjust antimicrobial sales and distribution data would allow the agency to assess trends in the amount of an antimicrobial drug class sold over 1 year for use in each of the four major food-producing species relative to that species' biomass for the same year. This differs from other published methods that use a biomass denominator that includes the biomass of each species added together. Also, while these other methods capture changes in animal populations, they don't capture variations in average weight over time. In contrast, FDA's proposed method incorporates annual changes in average weight.

Additional benefits of the proposed method are that it:

- Allows for a more detailed understanding of the amount of an antimicrobial drug class that is sold or distributed for use in each of the four major food-producing species relative to the species' biomass for a single year;

- Allows FDA to assess annual percent change in antimicrobial sales relative to annual variations in target animal biomass.
- Allows FDA to evaluate changes in sales and distribution data and target animal biomass. The agency may be able to assess the amount of drugs sold or distributed for use in food-producing animals compared to shifts in animal weights and populations; and
- Provides the option to separate out antimicrobial sales and distribution data for specific production classes. The agency may be able to compare annual changes in the mg/TAB values for products labeled for use in one production class within a species versus products labeled for use in the larger species group. The agency may also be able to assess the relative contributions of specific drugs to the total amount of sales of an antimicrobial drug class.

Three important limitations to the proposed method are:

- Sales and distribution data do not necessarily correspond to actual antimicrobial use in animals;
- It does not account for extralabel uses; and
- The biomass adjustment captures only those changes in management practices and production that affect annual animal numbers or average weights.

Request for Comments

FDA is seeking comments from the public on the proposed methodology. FDA is specifically asking stakeholders for input on the following questions:

1. Are the data sources identified appropriate? Are there other sources of data on animal populations and weights not referenced here that FDA should consider incorporating into the proposed method?
2. The proposed method uses the following formula:

   mg/TAB = (the sum of all sales of an antimicrobial drug class, in mg, for a given target animal species)/(estimated number of the given target animal species * estimated average weight, in kg, of this species)

   Is this mg/TAB formula appropriate for adjusting antimicrobial sales and distribution data relative to the size of the animal population potentially being treated with those drugs? If not, what are alternative biomass adjustment methods?

3. Does the proposed format for presenting the adjusted data provide an appropriate way to look for trends in sales for use of antimicrobials in major food-producing animals? Are there other ways that FDA can present the data?

4. Should FDA consider additional methods besides biomass to adjust antimicrobial sales data relative to the U.S. livestock population that are not referenced here? Please provide examples.