DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

APR 2 8 2011

APR 1 9 2011

The Honorable Louise M. Slaughter
House of Representatives
Washington, D.C. 20515-3221

Dear Ms. Slaughter:

Thank you for your letter of December 29, 2010, regarding antimicrobial resistance. The Food and Drug Administration (FDA or the Agency) is very concerned about preserving the effectiveness of current antimicrobials which are vital to protecting human and animal health against infectious microbial pathogens.

In your letter, you raise the following recommendations regarding the Agency's surveillance of antibiotic usage including: (1) expanding public reporting on antibiotic usage in the agricultural sector by providing more detail on classes critical to human medicine, (2) increasing reporting on the route of antibiotic administration in order to shed light on the pervasiveness of sub-therapeutic usage in agriculture, and (3) enhancing reporting on antibiotics produced for human use.

In response to your request, we have included the data on antimicrobial sales and distribution that are more detailed than those reported in FDA's 2009 summary report, *Antimicrobials Sold or Distributed for Use in Food-Producing Animals*, published in compliance with section 105 of the Animal Drug User Fee Amendments of 2008 (ADUFA 105). While we are providing most of the requested data, please be aware that any totals provided are subject to many of the important caveats outlined in the paragraphs below.

Unfortunately, the data you requested regarding certain subsets of the "Not Independently Reported" (NIR) group in the ADUFA Report includes nine classes of antimicrobials that, in accordance with confidentiality provisions in ADUFA, could not be reported separately. However, we are able to provide the distribution data on (1) fluoroquinolones and diaminopyrimidines combined, and (2) the combination of those antimicrobials used only in animal medicine (aminocoumarins, glycolipids, and quinoxalines). Those data are 11,101 kg and 802,388 kg, respectively.

The requested ADUFA 105 summary data reported by route of administration, specifically: (1) in feed, (2) in water, and (3) by injection are: 9,701,180 kg, 2,065,433 kg, and 422,818 kg, respectively. However, as noted in the bulleted list, the route of use cannot be used as a simple proxy for indication.

The ADUFA 105 summary data cannot be further subdivided into four groups by degree of importance in human medicine as you requested. The data needed to generate the disclosures above (route of administration data, and specific data for fluoroquinolones and diaminopyrimidines) were readily obtained from the ADUFA 105 sponsor submissions themselves, and a list of the antimicrobials that are used only in animal medicine is publicly available through the National Library of Medicine's DailyMed database. As such, these data are factual reports that reflect what is known about the various drug classes that were reported under ADUFA 105 without any need for further interpretation. In contrast, further subdividing these data by degree of importance in human medicine, per your second request, would involve an interpretive analysis that the Agency is not prepared to make in the context of providing antibiotic sales and distribution data. FDA intends to address this issue in an upcoming draft guidance which will be the companion to our recently published guidance on antimicrobial use in animals entitled *The Judicious Use of Medically Important Antimicrobial Drugs in Food Producing Animals* (GFI #209). This next guidance will propose more specific information on approaches for implementing the recommendations outlined in GFI #209, including clarifying the definition of the term "medically important" antimicrobial.

In preparing the first ADUFA 105 summary report for 2009, FDA adhered closely to the reporting requirements set forth in the statute. However, FDA agrees there may be alternative approaches to summarizing the ADUFA 105 sales and distribution data. Prior to making significant changes to the content and format of our annual summary reports, we intend to seek public comment on this issue when we publish proposed implementing regulations for ADUFA 105. Such rulemaking would incorporate the new ADUFA 105 reporting requirements into the existing records and reports regulations for new animal drugs, as well as the provisions for the Agency's annual summary report.

In response to your request that FDA publicly report the quantity and type of antibacterial drugs used in human medicine, we have included estimates of antibacterial drug sales based on IMS Health, IMS National Sales Perspectives™ data. It is important to note that these sales data represent the volume of product being sold to the various outlets from the manufacturer (i.e., "in the back door"), and not the volume of product being sold by the outlets to patients (i.e., "out the front door"). Similarly, the animal data represent a summary of the volume of product sold or distributed (through various outlets) by the manufacturer, and not the volume of product purchased by the end user for administration to animals. We have attached a copy of a report that summarizes these data. Importantly, as we have continued to consider these data, it has become apparent that there are a number of differences in the circumstances of use of antibacterial drugs in human and veterinary medicine that must be carefully considered, including:

- The number of humans in the population compared to the number of animals in each of the many veterinary populations (veterinary data provided to FDA are not broken down by species)
- Differences in physical characteristics of humans compared to various animal species (e.g., weight)

- Antibacterial drug use in humans can be for the treatment or prevention of an infection, whereas animal use may include treatment, control, prevention, and growth promotion. The available animal data are not reported to the FDA by indication and so do not allow us to distinguish between or among these different types of uses. For example, the majority of antimicrobial drugs used in animal feed are approved for both therapeutic and production purposes. Therefore, the route of use cannot be used as a simple proxy for indication.
- Milligram dosages for different antibacterial drugs differ (e.g., the usual adult human dosage for amoxicillin is different from the usual adult dosage for doxycycline). Total weights across different antibacterial drug classes (and even, to a lesser extent, within classes) are therefore difficult to interpret.
- Duration and dosage of antibacterial drug administration may also vary by indication and, in general, will also vary between the various animal species and humans.

With the above points in mind, it is difficult to draw definite conclusions from any direct comparisons between the quantity of antibacterial drugs used in humans and the quantity used in animals.

Thank you again for contacting us concerning this important matter. If you have further questions, please let us know.

Sincerely,

for Karen Meister
Supervisory Congressional
Affairs Specialist

Enclosure

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	November 30, 2010
To:	Edward Cox, M.D. Director Office of Antimicrobial Products
Through:	Gerald Dal Pan, M.D., MHS Director Office of Surveillance and Epidemiology
	Judy Staffa, Ph.D. Acting Director Division of Epidemiology Office of Surveillance and Epidemiology
From:	Grace Chai, Pharm.D. Acting Drug Use Data Analyst Team Leader Division of Epidemiology Office of Surveillance and Epidemiology
Subject:	Sales of Antibacterial Drugs in Kilograms
Drug Name(s):	Antibacterial Drugs
Application Type/Number:	Multiple
Applicant/sponsor:	Multiple
OSE RCM #:	2010-2472

1 INTRODUCTION

The Center for Veterinary Medicine is evaluating data on the use of antibacterial drugs in food-producing animals. The Office of the Commissioner has requested antibacterial drug use data in humans as a comparator. In support of FDA's efforts, the Division of Epidemiology (DEPI) has been requested to provide sales data of antibacterial drugs in kilograms to various retail and non-retail channels of distribution as a surrogate for nationwide antibacterial drug use in humans.

2 METHODS AND MATERIALS

2.1 DATA SOURCES USED

Proprietary drug use databases licensed by the Agency were used to conduct this analysis (*see **Appendix 1** for full data description*). IMS Health, IMS National Sales Perspectives™ was used to provide sales data of selected antibacterial drugs in kilograms distributed in the U.S. market to various retail and non-retail channels of distribution. These sales data represent the volume of product being sold to the various outlets from the manufacturer (e.g., "in the back door"), and not the volume of product being sold by the outlets to patients (e.g., "out the front door").

The number of kilograms sold were reported for the active molecule, regardless of formulation (I.V., oral, topical, etc). In addition, the data were reported for the total number of kilograms sold of the active molecule, single-ingredient and combination products combined. For example, the number of kilograms sold of amoxicillin included kilograms sold of single-ingredient amoxicillin and amoxicillin from combination products, such as amoxicillin-clavulanate. Additional combination products reported by the single active ingredient were: ticarcillin-clavulanate, ampicillin-sulbactam, piperacillin-tazobactam, imipenem-cilastatin, quinupristin-dalfopristin, and trimethoprim-sulfamethoxazole.

All data in this analysis have been cleared for public use by IMS Health, IMS National Sales Perspectives™.

3 RESULTS

3.1 SALES DATA BY SETTING OF CARE

IMS Health, IMS National Sales Perspectives™ was used to determine the various retail and non-retail channels of distribution for antibacterial drugs. Examination of wholesale data by number of kilograms sold in year 2009 indicated that the majority of antibacterial drugs were sold to retail pharmacy settings, accounting for approximately 75% of antibacterial drugs sold, followed by non-retail settings at 24% (mainly to hospitals) and mail order settings at 1% *(data not shown)*[1]

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[1] IMS Health, IMS Nationals Sales Perspectives™, Year 2009. Data extracted 11/10. File: 1011abx7.xls

3.2 *Sales Data by Drug Class and Molecule*

Table 1 shows the total number of kilograms sold of selected antibacterial drugs by drug class and molecule. There were approximately 3.3 million kilograms of antibacterial drugs sold in the U.S. market during year 2009. The penicillin drug class accounted for the largest proportion of kilograms sold accounting for approximately 44% of the market (1.5 million kilograms sold). Amoxicillin accounted for the highest number of kilograms sold with approximately 1.1 million kilograms sold in year 2009. The total number of kilograms sold for amoxicillin included amoxicillin from single-ingredient amoxicillin and combination products of amoxicillin-clavulanate.

Table 1, Part 1: Sales of Antibacterial Drugs by Drug Class and Molecule in Number of Kilograms Sold in Year 2009

Antibacterial Drug Class	**Years 2009**	
Drug name	**Sales in Kilograms**	**Kg Share %**
Grand Total	**3,316,906**	**100.0%**
-Penicillins	1,459,219	44.0%
Amoxicillin	1,123,551	77.0%
Piperacillin	142,849	9.8%
Penicillin V	130,953	9.0%
Ampicillin	41,962	2.9%
Dicloxacillin	7,936	0.5%
Nafcillin	6,262	0.4%
Oxacillin	2,875	0.2%
Ticarcillin	2,833	0.2%
Penicillin G	2.56E+13 (I.U.)	--
Mezlocillin		0.0%
Azlocillin		0.0%
Carbenicillin		0.0%
Cloxacillin		0.0%

Source: IMS Health, IMS Nationals Sales Perspectives™, Year 2009. Data extracted 11/10. File: 1011abx8.xls
*Beta-lactamase inhibitors that are part of a beta-lactam/beta-lactamase inhibitor combination (e.g., clavulanic acid, tazobactam, and sulbactam) and cilistatin are not included in this table. See text for how combination molecules are quantitated.

Table 1, Part 2: Sales of Antibacterial Drugs by Drug Class and Molecule in Number of Kilograms Sold, Year 2009

Antibacterial Drug Class	Years 2009	
Drug name	Sales in Kilograms	Kg Share %
- Cephalosporins	499,616	15.1%
--First generation	357,828	71.6%
Cephalexin	306,928	85.8%
Cefazolin	38,705	10.8%
Cefadroxil	12,196	3.4%
Cephalothin		0.0%
Cephapirin		0.0%
Cephradine		0.0%
--Second generation	49,103	9.8%
Cefuroxime axetil	26,224	53.4%
Cefprozil	11,578	23.6%
Cefaclor	4,542	9.3%
Cefoxitin	4,404	9.0%
Cefuroxime	1,548	3.2%
Cefotetan	807	1.6%
Cefamandole		0.0%
Cefonocid		0.0%
Cefmetazole		0.0%
Loracarbef		0.0%
--Third generation	81,018	16.2%
Cefdinir	40,874	50.4%
Ceftriaxone	28,604	35.3%
Ceftazidime	5,697	7.0%
Cefotaxime	2,683	3.3%
Cefixime	1,503	1.9%
Cefpodoxime (proxetil)	1,059	1.3%
Cefditoren (pivoxil)	535	0.7%
Ceftibuten	65	0.1%
Ceftizoxime	0	0.0%
Cefoperazone		0.0%
Moxalactam		0.0%
--Fourth generation	11,667	2.3%
Cefepime	11,667	100.0%
-Sulfa and TMP	471,442	14.2%
Sulfamethoxazole	386,002	81.9%
Trimethoprim	78,763	16.7%
Sulfadiazine	4,847	1.0%
Sulfisoxazole	1,830	0.4%
-Quinolones	304,741	9.2%
Ciprofloxacin	220,115	72.2%
Levofloxacin	68,108	22.3%
Moxifloxacin	15,418	5.1%
Ofloxacin	679	0.2%
Norfloxacin	257	0.1%
Gemifloxacin	163	0.1%
Naladixic acid		0.0%
- Macrolides	176,278	5.3%
Azithromycin	90,317	51.2%
Clarithromycin	54,542	30.9%
Erythromycin	31,419	17.8%
Dirithromycin		0.0%

Source: IMS Health, IMS Nationals Sales Perspectives™, Year 2009. Data extracted 11/10. File: 1011abx8.xls
*Beta-lactamase inhibitors that are part of a beta-lactam/beta-lactamase inhibitor combination (e.g., clavulanic acid, tazobactam, and sulbactam) and cilistatin are not included in this table. See text for how combination molecules are quantitated.

Table 1, Part 3: Sales of Antibacterial Drugs by Drug Class and Molecule in Number of Kilograms Sold, Year 2009

Antibacterial Drug Class	Years 2009	
Drug name	Sales in Kilograms	Kg Share %
-Tetracyclines	131,137	4.0%
Doxycycline	59,535	45.4%
Tetracycline	48,206	36.8%
Minocycline	22,063	16.8%
Demeclocycline	1,180	0.9%
Tigecycline	153	0.1%
Oxytetracycline	0	0.0%
-Nitroimidazoles	109,963	3.3%
Metronidazole	109,022	99.1%
Tinidazole	941	0.9%
- Lincomsamides	69,737	2.1%
Clindamycin	69,415	99.5%
Lincomycin	323	0.5%
-Carbapenems/penems	12,942	0.4%
Meropenem	5,246	40.5%
Imipenem	3,343	25.8%
Ertapenem	3,171	24.5%
Doripenem	1,182	9.1%
-Aminoglycosides	9,381	0.3%
Neomycin	5,459	58.2%
Tobramycin	1,868	19.9%
Gentamicin	1,155	12.3%
Amikacin	532	5.7%
Kanamycin	287	3.1%
Paromomycin	51	0.5%
Streptomycin	28	0.3%
Spectinomycin		0.0%
-Oxalozolidinones	5,487	0.2%
Linezolid	5,487	100.0%
-Monobactams	2,618	0.1%
Aztreonam	2,618	100.0%
-Lipopeptides	1,115	0.0%
Daptomycin	1,115	100.0%
-Ketolides	101	0.0%
Telithromycin	101	100.0%
-Streptogrammins	39	0.0%
Dalfopristin	27	70.1%
Quinupristin	12	29.9%
-Others	63,092	1.9%
Vancomycin	36,187	57.4%
Nitrofurantoin	18,842	29.9%
Rifampin	7,343	11.6%
Fosfomycin	529	0.8%
Colistin	138	0.2%
Chloramphenicol	51	0.1%
Telavancin	3	0.0%
Colistimethate sodium		0.0%
Polymixin B	1.14E+12 (I.U.)	--

Source: IMS Health, IMS Nationals Sales Perspectives™, Year 2009. Data extracted 11/10. File: 1011abx8.xls
*Beta-lactamase inhibitors that are part of a beta-lactam/beta-lactamase inhibitor combination (e.g., clavulanic acid, tazobactam, and sulbactam) and cilistatin are not included in this table. See text for how combination molecules are quantitated.

4 LIMITATIONS

Findings from this review should be interpreted in the context of the known limitations of the databases used. We estimated that the majority of sales in kilograms of antibacterial drugs were distributed primarily to the outpatient retail setting based on the IMS Health, IMS National Sales Perspectives™. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution. The amount of product purchased by these retail and non-retail channels of distribution may be a possible surrogate for human use, if we assume the facilities purchase drugs in quantities reflective of actual patient use.

5 CONCLUSIONS

Sales data in kilograms sold for selected antibacterial drugs were obtained as a surrogate of human antibacterial drug use in the U.S. market. Approximately 3.3 million kilograms of antibacterial drugs were sold in year 2009. The sales data were provided as a surrogate for human use to compare to antibacterial drug use in animals provided by sponsors.

APPENDIX 1: DATABASE DESCRIPTIONS

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.