DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Antimicrobial Animal Drug Sales and Distribution Reporting

Docket No. FDA-2012-N-0447

Preliminary Regulatory Impact Analysis

Initial Regulatory Flexibility Analysis

Unfunded Mandates Reform Act Analysis

Economics Staff

Office of Planning

Office of Policy, Planning, Legislation and Analysis

Office of the Commissioner

I. Introduction and Summary

FDA has examined the impacts of the proposed rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104-4). Executive Orders 12866 and 13563 direct Agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The Agency believes that this proposed rule is not an economically significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act requires Agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because the proposed rule would impose average annualized costs that amount to less than 0.01 percent of average annual revenues on those small entities that sponsor new animal drug applications, FDA has determined that the proposed rule, if finalized, would not have a significant economic impact on a substantial number of small entities. Therefore, this analysis of impacts and other sections of the preamble constitute FDA's initial regulatory flexibility analysis.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that Agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is $141million, using the most current (2013) Implicit Price

Deflator for the Gross Domestic Product. FDA does not expect this proposed rule to result in any 1-year expenditure that would meet or exceed this amount.

II. Objective and Description of the Proposed Rule

This proposed rule would amend the Agency's existing records and reports regulation in part 514 (21 CFR 514) to incorporate the sales and distribution data reporting requirements specific to antimicrobial new animal drugs. These requirements were added to the Federal Food, Drug, and Cosmetic Act (FD&C Act) by section 105 of the Animal Drug User Fee Amendments of 2008 (ADUFA 105). This proposal also includes an additional reporting provision intended to further enhance FDA's understanding of antimicrobial animal drug sales intended for use in specific food-producing animal species.

The proposed rule, if finalized, would amend the records and reports regulation in part 514 (21 CFR 514) by including procedures relating to the submission to FDA of annual sales and distribution data reports by sponsors of approved antimicrobial new animal drug products sold or distributed for use in food-producing animals. The proposal includes specific reporting criteria, including the requirement that sponsors submit species-specific estimates of product sales as a percentage of total sales. It also includes procedures applicable to FDA's preparation and publication of annual summary reports, based on the reports of the data the Agency receives from sponsors of approved antimicrobial new animal drug products sold or distributed for use in food-producing animals. Further, the proposal includes specific parameters for the content of the annual summary reports as well as explicit provisions intended to protect confidential business information and national security. And lastly, it contains provisions that would give sponsors of

approved antimicrobial new animal drug products the opportunity to avoid duplicative reporting of product sales and distribution data to the FDA under part 514.

A. ADUFA Background

Section 105 of ADUFA (Public Law 110-316) amends section 512(l) of the FD&C Act (21 U.S.C. 360b(l)) by adding new section 512(l)(3). Section 512(l) of the FD&C Act (21 U.S.C. 360b(l)) requires sponsors of approved or conditionally approved new animal drug applications to establish and maintain records and make such reports to FDA of data and other information relating to experience with their new animal drugs as required by regulation or order. Under new section 512(l)(3) of the FD&C Act, sponsors of approved antimicrobial new animal drugs must submit to FDA on an annual basis a report specifying the amount of each antimicrobial active ingredient in the drug that is sold or distributed for use in food-producing animals. Specifically, sponsors are required to report the amount of each antimicrobial active ingredient as follows: (1) By container size, strength, and dosage form; (2) by quantities distributed domestically and quantities exported; and (3) for each dosage form, a listing of the target animals, indications, and production classes that are specified on the approved label of the product. The information must be reported for the preceding calendar year, include separate information for each month of the calendar year, and be submitted to FDA each year no later than March 31. Section 512(l)(3) of the FD&C Act also requires FDA to publish an annual summary report of the antimicrobial drug sales and distribution data it collects from sponsors, and further provides that such data must be reported by antimicrobial class.

The first reporting year under new section 512(l)(3) of the FD&C Act was 2009. In accordance with the new law, sponsors of affected new animal drug products submitted their 2009 sales and distribution data to FDA by March 31, 2010, and FDA published a summary

report of these data later that same year. To date, FDA has collected sales and distribution data, and published summary reports of such data by antimicrobial class, for each calendar year from 2009 through and including 2012. As noted earlier, the purpose of this rulemaking is to amend FDA's animal drug records and reports regulation at part 514 to include administrative practices and procedures for sponsors of antimicrobial new animal drugs sold or distributed for use in food-producing animals who must report under section 512(l)(3) of the FD&C Act, including a proposed provision intended to enhance FDA's understanding of antimicrobial animal drug sales intended for use in specific food-producing animal species.

FDA previously issued an Advance Notice of Proposed Rulemaking (ANPRM) to obtain public input on potential amendments to its animal drug records and reports regulation at part 514, including the proposed provision to require sales and distribution data about specific food-producing animal species discussed below. FDA considered the comments it received in response to the ANPRM in preparing this proposed rule.

III. Summary of Preliminary Regulatory Impacts Analysis

A. Industry Costs

FDA estimates one-time costs to industry from this proposed rule, if finalized, at about $138,800. FDA estimates annual costs at about $55,700. These costs equate to an estimated total annualized cost of about $75,400 at a seven percent discount rate over 10 years and about $71,900 at a three percent discount rate over 10 years (table 1). The total annualized costs include the administrative cost to review the rule ($9,700) plus the cost to request the change of date and prepare the special one-time Drug Experience Report (DER) ($4,800) plus the cost of

providing the species-specific estimate of the percent of the drug product distributed domestically ($61,000).

B. Benefits

The proposed rule would introduce efficiency improvements into the new animal drug records and reporting process. It would also enhance FDA's understanding of antimicrobial animal drug sales intended for use in specific food-producing animal species and their contribution to the emergence or selection of antimicrobial resistant bacteria.

The proposed rule would provide some flexibility for the manner in which new animal drug sponsors report the sales and distribution data under both § 514.80 and proposed § 514.87, by allowing for only one set of report submissions under certain circumstances. FDA estimates that this will reduce labor costs for new animal drug sponsors by $100,200 annually.

Another benefit of this proposed rule would be the cost savings associated with reporting monthly sales and distribution data in terms of units of product sold or distributed rather than calculating the amount of antimicrobial active ingredients associated with these monthly product sales and distribution data. FDA estimates the calculation reductions would amount to an annual benefit of about $18,600. FDA estimates total annual benefits at about $118,800.

Table 1.--Costs and Benefits of Proposed Rule ($ million)

	1-Time Cost and Benefits	Total Annualized Costs and Benefits at 7%[1]
Industry Costs	$138, 800	$75,400
Government Costs		N/A
Industry Benefits		$118,800

[1]Total annualized costs and benefits are equal to annualized one-time cost at 7 percent over 10 years.

In table 2, FDA provides the Regulatory Information Service Center/Office of Information and Regulatory Affairs Consolidated Information System accounting information.

Table 2.--Economic Data: Costs and Benefits Statement

				Units			
Category	Primary Estimate	Low Estimate	High Estimate	Year Dollars	Discount Rate	Period Covered	Notes
Benefits							
Annualized	$0.119				7%		
Monetized $millions/year	$0.119				3%		
Annualized Quantified					7%		
					3%		
Qualitative							
Costs							
Annualized	$.075				7%		
Monetized $millions/year	$.075				3%		
Annualized Quantified					7%		
					3%		
Qualitative							
Transfers							
Federal					7%		
Annualized Monetized $millions/year					3%		
From/To	From:			To:			
Other					7%		
Annualized Monetized $millions/year					3%		
From/To	From:			To:			
Effects							
State, Local or Tribal Government: No Effect							
Small Business: No effect							
Wages: No estimated effect							
Growth: No estimated effect							

IV. Need for Regulation

Antimicrobial resistance, and the resulting failure of antimicrobial therapies in humans, is a mounting public health problem. This phenomenon is driven by many factors, including the use of antimicrobial drugs in both humans and animals. Due to the use of medically important antimicrobials in food-producing animals, food-borne bacteria may become resistant to antimicrobial drugs used to treat disease in humans. As a consequence, antimicrobial resistant food-borne pathogens may infect humans and thereby reduce the effectiveness of antimicrobial therapies in some people. These antimicrobial resistant food-borne pathogens are an external cost to the producers of food-producing animals and would therefore not be incorporated into private costs of production.

Although antimicrobial resistance is growing, we do not know how much the use of medically important antimicrobials in food-producing animals contributes to the phenomenon. Without more information, both the cause and extent of antimicrobial resistance associated with the use of these products may not be fully appreciated. Food animal producers, veterinarians, and animal drug sponsors have no incentives to monitor certain uses of antimicrobial animal drugs and how that use may lead to the growth of antimicrobial resistant bacteria. The transaction costs for any individual food animal producer, veterinarian, or animal drug sponsor to gather or disseminate this information would exceed any private benefits. As part of the effort to address the problem of antimicrobial resistance, FDA needs additional information on antimicrobial animal drug use in food-producing animals, including information on the sales of these animal drug products, as well as the distribution of the sales of these products among the various animal species for which they are intended for use.

Because the antimicrobial sales and distribution data reported to FDA by drug sponsors under section 512(l)(3) of the FD&C Act are derived from drug product sales, very little can be concluded about antimicrobial sales intended for use in any one particular species for products that are approved for use in more than one species. Having species-specific estimates of product sales and distribution for use in the four major food-producing categories of animal species (cattle, swine, chickens, turkeys) would be important in supporting efforts such as the National Antimicrobial Resistance Monitoring System (NARMS), a surveillance program that tracks trends related to antimicrobial resistance in food-producing animals and humans. This additional sales and distribution data could inform microbial food safety risk assessments by providing a better indication of the extent to which a drug or drug class is used in a specific food animal species by a specific route of administration. From this data, it may be possible to draw conclusions about how antimicrobial sales and distribution data compare with data from NARMS. In addition, such information could further enhance FDA's ongoing activities related to slowing the development of antimicrobial resistance and is consistent with the recommendations in guidance recently issued by this Agency addressing the judicious use of medically important antimicrobial drugs in food-producing animals (Guidance for Industry #209, entitled "The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals").

These proposed regulations would provide specific reporting criteria for sponsors of approved antimicrobial new animal drug products who must report data on the sales and distribution of their products for use in food-producing animals to FDA, as required by section 512(l)(3) of the FD&C Act. These proposed regulations would also provide for reporting of some additional information regarding the sales and distribution of antimicrobial products

intended for use in specific species of food-producing animals. Currently, most antimicrobial new animal drug products that are approved for use in food-producing animals are labeled for use in more than one animal species, in some cases, 5 or more species.

V. Benefits of the Proposed Rule

The benefits of this proposed rule, if finalized, result from an efficiency introduced by two of its provisions (as noted in section III.B.), as well as the value of the estimated species-specific antimicrobial drug sales and distribution data for use in the study of the development of antimicrobial resistant bacteria in animals (as noted in section IV.). This change is expected to result in a reduction in current compliance costs.

The current practice for compliance with ADUFA 105 includes the sponsors' calculations of the specific amounts of antimicrobial active ingredients associated with monthly product sales and distribution data. FDA includes language in the preamble to proposed § 514.87 that explains the basis for FDA's proposal that sponsors no longer calculate nor provide the antimicrobial active ingredient amounts in their antimicrobial drug sales and distribution data reports to FDA. The accuracy of industry reporting of this calculation shows great variability, causing additional verification efforts for FDA personnel. Therefore, it would be more efficient for sponsors to limit their annual reporting to product sales and distribution data, and allow FDA to calculate the exact amounts of antimicrobial active ingredients associated with those product sales. FDA estimates that this would reduce the industry reporting effort by one hour per application. FDA estimates that 153 active (i.e., currently marketed) applications for antimicrobial new animal drugs that are sold or distributed for use in food-producing animals would be affected by this change in policy, resulting in 153 fewer compliance hours annually. FDA assumes that one-half of the firms would

use general or operations managers (at small to mid-sized firms), and one-half of the firms would use industrial production managers (at larger firms) to make this calculation. The Bureau of Labor Statistics (BLS) list the average labor rate for general and operations managers under the North American Industrial Classification System (NAICS) code 325400 – Pharmaceutical and Medicine Manufacturing, at about $67 per hour for 2012. FDA adjusts this wage for overhead and other benefits by 100 percent, which results in an adjusted wage rate of about $134 per hour. BLS lists the average labor rate for industrial production managers under NAICS code 325400 at about $54 per hour for 2012. FDA adjusts these wages for overhead and other benefits by 100 percent, which results in an average adjusted wage rate to about $109 per hour. The annual benefit of the reduction of 153 hours times an average of $121 per hour is about $18,600.

Another provision of this rule which would lead to a cost savings is the provision that would give sponsors the option to not report distribution data under current § 514.80(b)(4)(i) for their approved applications that include the same products for which antimicrobial drug sales and distribution data would need to be reported under proposed § 514.87. FDA estimates that 90 percent of the sponsors that currently market approved new animal drugs containing an antimicrobial active ingredient for use in food-producing animals would make the request to change the submission date for their annual periodic drug experience report such that the reporting period begins on January 1 and ends on December 31, as provided in proposed § 514.87. These 138 approved applications (90 percent of 153) would still have to account for the costs of data collection and preparation, but they would no longer be required to include distribution data along with the other information required in the Drug Experience Report (DER) under proposed § 514.80(b)(4)(i)(B). FDA estimates that the time saved per application from the removal of the requirement for the distribution data in the DER could be as much as six hours

per application. Using the same adjusted wage rates and distribution of hours by adjusted wage rates (one-half of the total hours at each rate), the annual benefit of the reduction of 138 hours times an average of $121 per hour is about $100,200. FDA acknowledges some uncertainty surrounding the average labor savings from this provision of the proposed rule.

The total annual benefit of this proposed rule is estimated at $118,800 ($18,600 plus $100,200).

VI. Compliance Costs

Because the first year of antimicrobial new animal drug sales and distribution data reported under ADUFA 105 was for calendar year 2009, sponsors of approved applications for antimicrobial new animal drugs sold or distributed for use in food-producing animals have been incurring compliance costs to gather the sales and distribution data, process the data, and prepare the annual reports on the amount of each antimicrobial active ingredient in the drug that is sold or distributed for use in food-producing animals for some time. Those compliance costs are not a direct result of this rule. However, we will describe them here, for illustrative purposes only, but not include them in the total cost estimates of this analysis.

A. Costs of ADUFA 105

FDA currently makes estimates of the compliance burden for the requirements of ADUFA 105 for use in periodic reports to OMB. For 2012, data was submitted by 23 sponsors of 153 active applications for antimicrobial animal drug products that are sold or distributed for use in food-producing animals, with an average of 6.7 active approvals per sponsor. FDA estimates that 60 hours are required to collect the necessary data and prepare a paper submission to FDA for each active application. FDA estimates that only 50 hours are required for each

electronic submission of the same information. FDA assumes paper submissions and electronic submissions each represent one-half of total submissions, resulting in a total of 8,415 labor hours for the industry. Industry personnel at either the general and operations manager level or at the industrial production manager level would conduct this effort.

The 2012 data also showed 11 sponsors with only inactive approved applications and 18 sponsors with both active and inactive approved applications together have 196 inactive approved applications for antimicrobial animal drug products for use in food-producing animals. FDA estimates that the sponsors of these 196 inactive applications only require 2 hours per approved application to prepare and submit the proposed report stating that there were no product sales for the year, regardless of whether it is submitted on paper or electronically. This labor effort would amount to 392 hours annually. The sum of all labor hours required for this provision amounts to 8,807 hours.

FDA again assumes that one-half of the firms would use general or operations managers (at small to mid-sized firms), and one-half of the firms would use industrial production managers (at larger firms) to collect the data and prepare the submission. If the combined 8,807 hours are evenly divided between the two adjusted wage rates, the current annual compliance costs of ADUFA 105 are about $1.07 million. If the data submitted for 2012 is representative of the data from 2009 through 2011, the annual costs that were incurred by industry from 2009 through 2011 would be similar, but none are considered a direct result of this proposed rule.

B. Administrative Costs of Proposed Rule

Current sponsors of approved or conditionally approved applications for new animal drugs containing an antimicrobial active ingredient that are sold or distributed for use in food-

producing animals would be expected to review the rule that would create the administrative practices and procedures and develop a plan to comply with the requirements. FDA believes that since the proposed rule would mostly codify current practices, sponsors would not require significant review time. FDA estimates that the same 34 sponsors (23 sponsors of active and inactive applications and 11 sponsors of only inactive applications) would need to review this rule and develop a compliance plan. This would require about 24 hours for each of the 23 sponsors with active approvals. A sponsor with only one or more inactive approvals is expected to do much less work since a compliance plan does not need to be developed; thus, FDA estimates that rule review for each of these sponsors would only take one hour. FDA again estimates that one-half of the sponsors would use personnel at either the general and operations manager level and one-half would use personnel at the industrial production manager level to perform the review and, to the extent necessary, develop a simple compliance plan.

FDA uses the same adjusted hourly pay for general and operations managers of about $134 per hour for the 24 hours of review for one-half, or 11.5 sponsors of active approvals. This results in a one-time compliance cost of about $36,900, which equates to an annualized cost of about $5,300 when discounted at 7 percent over 10 years. Using the same adjusted hourly pay for industrial production managers of about $109 per hour, the 24 hours of review for the other 11.5 sponsors of active approvals would impose a one-time compliance cost of about $30,100. This equates to an annualized cost of about $4,300 when discounted at seven percent over ten years.

For the one-hour review time for sponsors of inactive approvals, FDA assigns one-half, or 5.5 hours, at the $134 per hour adjusted rate for general and operations managers. The review for the other 5.5 hours is assigned at the adjusted rate for industrial production managers of $109 per hour. The total cost for the review by sponsors of inactive approvals is estimated at about

$1,300, which equates to an annualized cost of about $200 when discounted at seven percent over ten years.

FDA estimates total administrative costs for rule review and compliance plans development to be about $68,300. This equates to $9,700 when discounted at seven percent over ten years (and about $8,000 when discounted at three percent over 10 years).

C. Conforming Changes to Proposed § 514.80

Proposed § 514.80(b)(4)(i)(B) rule would allow applicants submitting annual sales and distribution reports for antimicrobial new animal drug products under § 514.87 the option to not report distribution data under proposed § 514.80(b)(4)(i)(A) for the approved applications that include these same products, but only provided certain specific conditions are met. One condition is that sponsors must ensure that the beginning of the reporting period for the annual periodic drug experience reports for such applications is January 1. For applications that currently have a reporting period that begins on a date other than January 1, applicants must request a change in reporting submission date for their annual periodic drug experience report such that the reporting period begins on January 1 and ends on December 31, as described in § 514.80(b)(4). A second, and related, condition is that applicants who change their reporting submission date must also, on a one-time basis, submit a special drug experience report, as described in current § 514.80(b)(5)(i), that addresses any gaps in distribution data caused by the change in reporting periods. The final condition with cost implications is that applicants who meet the criteria under § 514.80(b)(4)(i)(B) and choose not to report under proposed § 514.80 (b)(4)(i)(A) must ensure that full sales and distribution data for each product approved under such applications are alternatively reported under § 514.87.

FDA estimates that 90 percent of the sponsors of that currently market approved new animal drugs containing an antimicrobial active ingredient for use in food-producing animals would make the request to change the submission date for their annual periodic drug experience report such that the reporting period begins on January 1 and ends on December 31. Ninety percent of 153 active applications equates to about 138 applications held by approximately 21 sponsors. FDA estimates that it would take about 2 hours for personnel to meet the first two conditions, making the change of date request for each application and preparing the one-time special drug experience report for each application. This results in 275 hours. At the overhead and other benefits-adjusted wage rate of about $134 per hour for general and operations manager for one-half of the hours, and at $109 per hour for industrial production managers for the other one-half of the hours, the one-time cost would be about $33,400. This equates to an annualized cost of about $4,800 when annualized over 10 years at a 7% discount rate (and about $3,900 at a three percent discount rate).

D. Costs of Proposed § 514.87

Proposed § 514.87(c) would require that antimicrobial sales and distribution data reports contain a species-specific estimate of the percentage of each antimicrobial new animal drug product that was sold or distributed domestically in the reporting year for use in any of the following four major food-producing animal species, but only for such of these species that appear on the approved label: cattle, swine, chickens, and turkeys. The total of the species-specific percentages reported for each product must account for 100% of its sales and distribution; therefore, a fifth category of “other species/unknown” would also be reported. This category would be used to capture the estimated percentage of each new animal drug product

that was sold or distributed for use in animal species other than the four major food-producing species or otherwise unknown to the reporting drug sponsor.

FDA estimates that an individual would spend about five hours complying with this requirement in the first year. Subsequent years are estimated to require about 3 hours to comply. The additional two hours in the first year is a one-time cost incurred as individual company personnel discuss and settle upon a method to calculate these species-specific estimates. With the labor split evenly over the two wage rates, these two hours amount to a one-time cost of about $37,100 for the 153 applications. This equates to $5,300 in annualized costs over 10 years at a 7 percent discount rate (and $4,400 at a 3 percent discount rate). Under the same assumptions, the three hours needed to gather the necessary information and calculate the percentage estimate would cost about $55,700 annually. The average total annualized cost for this provision over 10 years would be about $61,000 ($5,300 annualized one-time cost plus the $55,700 annual cost).

E. Total Industry Costs

In table 3, total one-time costs for this proposed rule, if finalized, are estimated at $138,800, about one-half of which are unavoidable costs for reviewing the rule and making a compliance plan. On an annualized basis, the cost of the rule is about $75,400 when discounted at 7 percent over 10 years ($71,900 at a 3% discount rate).

Table 3.--Industry Compliance Costs[1]

Type of Cost	1-Time Cost	Annual Cost	Annualized Cost
Administrative Review of the Rule	$68,300		$9,700
Request a Change of Date and Submit Special Drug Experience Report	$33,400		$4,800
Report Species-Specific Estimate of Percent of Products Distributed Domestically	$37,100	$55,700	$61,000
Total Industry Costs	$138,800	$55,700	$75,400

[1]Columns may not add to total costs due to rounding.

F. Government Costs

FDA estimates that the review of annual reports submitted by sponsors of new animal drugs containing antimicrobial active ingredients and the preparation and publication of FDA's annual summary report required under proposed § 514.87(f) would require four additional full-time employees. Based on the Fiscal Year 2010 appropriation for the Center for Veterinary Medicine at FDA, the average annual cost of one of these employees is $213,000, including the cost of all overhead support for, and benefits to, that full time employee. This equates to an hourly wage of about $100. FDA estimates the cost of these four employees is about $852,000. FDA emphasizes that the great majority of these costs are already being incurred because sponsors have been required to annually report antimicrobial sales and distribution data as required by ADUFA 105 since March 2010 (data covering calendar year 2009). FDA does not expect the cost to administer this program will change significantly should the provisions in this proposed rule be finalized.

VII. Analysis of Alternatives

An alternative to the proposed rule that would require a slightly larger effort by the sponsor would be to include reporting of the methodology used to estimate the species-specific estimate of the percentage of each product distributed domestically. FDA considered including this provision in the proposed rule. In the end, FDA decided not to include it because it would not add to the quality or timeliness of the data submitted, and could be seen as adding an additional burden to industry. FDA has not estimated this burden but thinks it would not have been significant.

VIII. Regulatory Flexibility Act

The Regulatory Flexibility Act requires Agencies to prepare a regulatory flexibility analysis if a rule is expected to have a significant economic impact on a substantial number of small entities. The discussion in this section and the previous sections of the economic analysis constitute the initial regulatory flexibility analysis of this proposed rule.

One requirement of the Regulatory Flexibility Act is a succinct statement of any objectives of the rule. As stated previously in the preamble to the proposed rule, FDA is issuing these administrative practices and procedures for animal drug sponsors who must report their sales and distribution data to FDA as required by ADUFA 105.

A. Description of Small Entities

The Regulatory Flexibility Act also requires a description of the small entities that would be affected by the rule, and an estimate of the number of small entities to which the rule would apply. The Small Business Administration (SBA) considers any pharmaceutical manufacturer (NAICS code 325412--Pharmaceutical Preparation Manufacturing, which includes Type A medicated article sponsors) with fewer than 750 employees to be small. Table 4 presents U.S. Census data from 2007. In 2007, there were 991 establishments in NAICS 325412. Approximately 92 percent to 98 percent of the establishments in NAICS code 325412 had fewer than 750 employees and would be considered small business establishments. However, those firms with multiple establishments that in total exceed 750 employees would reduce the percent of firms that are considered small businesses. In any case, FDA believes that a substantial number of firms in NAICS 325412 could qualify as small business entities.

Table 4 also illustrates the distribution of revenues by type and size of manufacturer establishment. Average annual revenues per firm for the pharmaceutical preparation

manufacturers range from less than $1.0 million for small firms with fewer than 5 employees to over $1 billion for large firms with 1,000 or more employees.

Table 4.--Establishments and Revenues for Pharmaceutical Preparation Manufacturers[1]

Employment size	No. of Establishments	Annual Value of Shipments ($ mil)	Average Annual Value of Shipment per Establishment ($ mil)
0-4	284	240.0	0.8
5-9	124	344.7	2.8
10-19	77	429.2	5.6
20-99	249	9,899.3	39.8
100-499	182	44,927.8	246.9
500+	75	87,035.2	1,160.5
Industry total	991	142,876.3	144.2

[1]2007 Economic Census

B. Costs to Small Entities

Table 5 shows the relative burden that establishments of different sizes can expect from the proposed rule. For pharmaceutical preparation manufacturers, both the one-time costs and annualized costs are less than 1 percent of the value of shipments for those establishments with zero to four employees. For those establishments with 100 or more employees, which are the type that are expected to sponsor new animal drug applications, the one-time an annual costs are less than 0.01 percent of the value shipments. FDA does not expect that this proposed rule would cause significant impacts on a substantial number of small entities.

Table 5 - Costs by Establishment Size for Pharmaceutical Preparation Manufacturers

Employment Size	No. of Establishments	One-Time Costs as a Percent of Average Revenues	Annualized Costs as a Percent of Average Revenues
NAICS-325412--Pharmaceutical Preparation Manufacturing			
0-4	284	0.71%	0.39%
5-9	124	0.21%	0.12%
10-19	77	0.11%	0.06%
20-99	249	0.02%	0.01%
100-499	182	<0.01%	<0.01%
500+	75	<0.01%	<0.01%