DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Defining ‘Small Number of Animals’ for Minor Use Determination; Periodic Reassessment

Docket No. FDA-2022-N-1128

Final Regulatory Impact Analysis
Final Regulatory Flexibility Analysis
Unfunded Mandates Reform Act Analysis

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I. Introduction and Summary

A. Introduction

We have examined the impacts of the direct final 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 (Pub. L. 104-4). Executive Orders 12866 and 13563 direct us 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). We believe that this direct final rule is not a significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because net costs of the direct final rule are less than 0.32 percent of average annual revenues for the smallest firms in the industry, we certify that the direct final rule will not have a significant economic impact on a substantial number of small entities.

The Unfunded Mandates Reform Act of 1995 (section 202(a)) requires us to prepare a written statement, which includes an assessment of anticipated costs and benefits, before issuing "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 $165 million, using the most current (2021) Implicit Price Deflator for the Gross Domestic Product. This direct final rule would not result in an expenditure in any year that meets or exceeds this amount.

B. Summary of Costs and Benefits

The direct final rule (rule) will increase the upper limit thresholds (i.e., "small numbers") for dogs and cats in the definition of "small number of animals" to reflect current market conditions related to drug development costs and drug treatment values[1] for purposes of determining eligibility for drug development incentives under the Minor Use and Minor Species Animal Health Act of 2004 (MUMS Act). By expanding incentives for new animal drug development under the MUMS Act, the rule could benefit pet owners by improving the health of dogs and cats with uncommon diseases or conditions. These health improvements could result from the earlier marketing of new animal drugs by sponsors that apply for and receive conditional approval as a result of the rule. The rule also could result in cost savings to new animal drug sponsors (sponsors) and FDA. Sponsors that receive conditional approval have the ability to market their new animal drug for up to 5 years, subject to annual renewals, before providing substantial evidence that it is effective, as required for full approval. This would defer associated costs to sponsors and FDA until later in the development process.

Because the rule could increase the number of uncommon diseases or conditions in dogs and cats that qualify for minor use drug development incentives—including user fee waivers,

[1] "Drug treatment value" means the portion of the actual cost paid for treating an animal with a given drug that goes to the sponsor of the drug.

exclusive marketing rights, grants, and eligibility for conditional approval—sponsors could incur costs to prepare and submit additional minor use determination requests and, for those sponsors that pursue designation for their new animal drug, annual designation reports to FDA. FDA will bear costs to review any additional minor use determination requests and annual designation reports. Potential sponsors of new animal drugs for minor uses in dogs and cats will also incur a one-time cost to read and understand the rule.

We additionally estimate potential within-industry transfers[2] from sponsors receiving user fee waivers as a result of the rule to fee-paying sponsors, and transfers from government to industry in the form of grants to support safety and effectiveness testing.

We summarize the annualized benefits and costs of the rule in Table 1. We estimate that the annualized benefits over 20 years will range from $0 to $6.06 million at a 7 percent discount rate, with a primary estimate of $3.03 million, and from $0 to $7.43 million at a 3 percent discount rate, with a primary estimate of $3.72 million. Annualized costs will range from $3,033 to $31,741 at a 7 percent discount rate, with a primary estimate of $17,387, and from $2,244 to $30,285 at a 3 percent discount rate, with a primary estimate of $16,264.

Table 1. Summary of Benefits, Costs, and Distributional Effects of the Rule

Category		Primary Estimate	Low Estimate	High Estimate	Units			Notes
					Year Dollars	Discount Rate	Period Covered	
Benefits	Annualized Monetized ($ millions/year)	$3.03	$0.00	$6.06	2021	7%	20 years	These include benefits to pet owners and cost savings to industry and FDA.
		$3.72	$0.00	$7.43	2021	3%	20 years	
	Annualized Quantified							
	Qualitative							
Costs	Annualized Monetized ($ millions/year)	$0.017	$0.003	$0.032	2021	7%	20 years	
		$0.016	$0.002	$0.030	2021	3%	20 years	
	Annualized Quantified							
	Qualitative							
Transfers	Federal Annualized Monetized ($ millions/year)	$0.43	$0.00	$0.86	2021	7%	20 years	
		$0.48	$0.00	$0.97	2021	3%	20 years	
		From: Government			To: Industry			
	Other Annualized Monetized ($ millions/year)	$0.47	$0.00	$0.94	2021	7%	20 years	
		$0.57	$0.00	$1.14	2021	3%	20 years	
		From: Industry			To: Industry			
Effects	State, Local, or Tribal Government: None. Small Business: Quantified effects of less than 0.32 percent of average annual revenues for the smallest firms. Wages: None. Growth: None.							

[2] Transfers are monetary payments between persons or groups that do not affect the total resources available to society (Ref. [14]).

II. Final Regulatory Impact Analysis

A. Background

1. MUMS Act

In 2004, the MUMS Act amended the Federal Food, Drug, and Cosmetic Act (FD&C Act) to provide incentives to support the development and approval of new animal drugs for the treatment of minor animal species and minor uses in major animal species. Incentives in the MUMS Act are meant to encourage sponsors to develop new animal drugs for such indications by making the development of these drugs more affordable.

In the MUMS Act, Congress defines a "minor use" to mean the intended use of a new animal drug in a major species for a condition that (1) occurs infrequently and in only a "small number of animals" each year or (2) in limited geographic areas and in only a "small number of animals" each year. The MUMS Act defines the major species of animals as dogs, cats, horses, cattle, swine, turkeys, and chickens. On March 18, 2008, we published a proposed rule to define the term "small number of animals" by establishing an upper limit threshold (i.e., small number) for each of the seven major species of animals to provide a means of determining whether an intended use of a new animal drug in one of these species qualifies as a minor use under the MUMS Act (Ref. [1]). We published the final rule, "Defining 'Small Number of Animals' for Minor Use Designation," on August 26, 2009 (Ref. [2]). Since publication of the August 2009 final rule, we have used the small numbers to make minor use determinations.

The MUMS Act includes incentives meant to encourage sponsors to develop more new animal drugs for minor species or for small treatment populations of major species (i.e., minor uses). While intended uses in minor species qualify for incentives by definition, for intended uses in major species to be eligible for these incentives, sponsors first must receive an affirmative minor use determination from our Center for Veterinary Medicine's (CVM) Office of Minor Use and Minor Species Animal Drug Development (OMUMS). To initiate a minor use determination from OMUMS, sponsors must prepare and submit a request containing supporting information about the new animal drug and its intended use.

When we defined the small numbers in the August 2009 final rule, we committed to reassessing them on a periodic basis. Based on our latest reassessment, we propose to increase the small numbers for dogs and cats due to relative changes in drug development and drug treatment costs for these species over time.

2. MUMS Act Provisions for Minor Uses in Major Species

The MUMS Act contains provisions intended to encourage the development of MUMS drugs. Two sections of the MUMS Act apply to the development of new animal drugs for minor uses in major species: conditional approval and designation.[3] In addition to the incentives

[3] See sections 571 and 573 of the FD&C Act, respectively.

provided by these provisions, sponsors of minor use drugs may also be eligible for waivers from certain user fees.

a. *Designation*

As authorized in section 573 of the FD&C Act, sponsors of designated MUMS drugs are eligible for grants from CVM to fund safety and effectiveness studies to support their drug's development, and 7 years of exclusive marketing rights beginning either upon conditional or full approval of the drug.[4] Designation requires sponsors to actively work toward approval of the drug and to submit annual reports to us to demonstrate their progress. We cannot grant more than one designation for the same drug, dosage form, and intended use. However, we can grant more than one designation for the same drug if the designations are for different intended uses or dosage forms. We can also designate different new animal drugs for the same intended use.

i. *Grants*

We have authority under section 573 of the FD&C Act to provide grants to animal drug sponsors to help cover the costs of certain expenses they may incur in connection with the development of designated MUMS new animal drugs. We currently allow sponsors of designated MUMS drugs to apply for grants from us twice per fiscal year to support safety and effectiveness studies. The maximum value of a single grant is $250,000 per year for a maximum of 2 years. We do not limit the number of grants sponsors can apply for during the development process.

ii. *Exclusive Marketing Rights*

The Generic Animal Drug and Patent Term Restoration Act of 1988 (GADPTRA) provides 5 years of marketing exclusivity for those applications providing for the first-time approval for animal use of a new chemical entity (NCE), or 3 years of marketing exclusivity for a new use of an approved drug, or where the chemical entity has already been approved in another application.[5] This marketing exclusivity offers protection from generic copying. The period of marketing exclusivity associated with GADPTRA begins on the date of full approval of the new animal drug application (NADA). In comparison, designated MUMS new animal drugs receive 7 years of exclusive marketing rights, which grant protection from approval of another application for the same drug in the same dosage form and for the same intended use, and from generic copying of the designated drug.[6] This 7-year period begins on the date when the MUMS drug is either approved or conditionally approved and, depending upon the circumstances, may overlap with some or all of the period of marketing exclusivity under GADPTRA.

b. *Conditional Approval*

[4] We additionally have authority under section 573 of the FD&C Act to enter into contracts with animal drug sponsors to help cover the costs of certain expenses they may incur in connection with the development of designated new animal MUMS drugs. However, we have not entered into any contracts with such sponsors at the time of this analysis. Therefore, we assume that increasing the small numbers for dogs and cats would not result in additional contracts with sponsors of designated drugs.

[5] See section 512(c)(2)(F) of the FD&C Act.

[6] See section 573 of the FD&C Act and the agency's regulation at 21 CFR 516.31.

The conditional approval provisions of the FD&C Act allow the sponsor of a MUMS drug that has received conditional approval to legally market the drug before collecting all of the effectiveness data needed for full approval, but only after demonstrating that the new animal drug is safe and that there is a "reasonable expectation" of its effectiveness for the intended use. The initial conditional approval is valid for 1 year with the potential for up to 4 annual renewals. For us to grant a renewal, the sponsor must demonstrate active progress toward collecting the remaining effectiveness data necessary to support the full approval of the drug. The sponsor must attain full approval within 5 years after receiving conditional approval, or the conditional approval will expire.

c. *User Fee Waivers*

Under the Animal Drug User Fee Act[7] (ADUFA), we collect four types of user fees:

1. One-time application fee, which we assess when a sponsor submits an application for conditional approval of a new animal drug (CNADA) or a NADA for full approval[8];
2. Annual establishment fee, which we begin to assess when an establishment starts to manufacture an approved or conditionally approved new animal drug for commercial distribution;
3. Annual product fee, which we begin to assess when a sponsor starts to market an approved or conditionally approved new animal drug; and
4. Annual sponsor fee, which we begin to assess when a person first meets the definition of an "animal drug sponsor."[9]

We grant waivers from or a reduction of these user fees under certain circumstances (waiver provisions). A sponsor may be eligible for a waiver from the one-time application fee under the MUMS waiver provision if the CNADA or NADA, or supplemental CNADA or NADA, is intended solely to provide for a MUMS indication.[10] Likewise, a sponsor may qualify for an annual product fee waiver under this same MUMS waiver provision if their animal drug product is solely for a minor species or a minor use in a major species.

For us to waive annual establishment fees, an establishment's entire portfolio of manufactured drug products must qualify for a waiver under one or more of the waiver provisions (MUMS, significant barrier to innovation, fees exceed costs, etc.).[11] Similarly, a sponsor may be eligible for a waiver from the annual sponsor fee if the sponsor's entire portfolio of Investigational New Animal Drug (INAD) files and animal drug applications is eligible for a waiver based on one or more waiver provisions. Thus, sponsors engaged in the development,

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[7] See the codified ADUFA provisions in sections 739, 740, and 740A of the FD&C Act.

[8] In cases where a sponsor who is submitting an NADA previously submitted a CNADA for the same drug product and paid an application fee at the time they submitted the CNADA, the sponsor does not have to pay another application fee when submitting the NADA as long as the NADA is submitted in accordance with the timeframe set forth in section 571(h) of the FD&C Act (see section 740(a)(1)(C)(ii)).

[9] In section 739(6) of the FD&C Act, Congress defines the term "animal drug sponsor" for purposes of ADUFA as "either an applicant named in an animal drug application that has not been withdrawn by the applicant and for which approval has not been withdrawn by the Secretary [of Health and Human Services], or a person who has submitted an investigational animal drug submission that has not been terminated or otherwise rendered inactive by the Secretary."

[10] See section 740(d)(1)(D) of the FD&C Act.

[11] See section 740(d) of the FD&C Act.

manufacturing, and marketing of MUMS drugs may or may not be eligible for waivers from all user fees. Additionally, sponsors requesting waivers from establishment, product, or sponsor fees must reapply for these waivers on an annual basis.

B. Need for Federal Regulatory Action

In passing the MUMS Act, Congress recognized a need for approved new animal drugs for use in minor species and for treating animal diseases and conditions that occur infrequently or in limited geographic areas.[12] It was generally not economically feasible for new animal drug applicants to pursue approvals for species, diseases, and conditions based on the small market shares, low-profit margins, and capital investment involved. The passage of the MUMS Act in 2004 put in place development incentives and other mechanisms to help address this problem.

To more precisely determine whether a new animal drug should be eligible for development incentives under the MUMS Act, we defined an upper threshold treatment population (small number) for each of the major animal species in the 2009 "Defining 'Small Number of Animals' for Minor Use Designation" final rule (Ref. [1]). For each major companion animal species, including dogs and cats, the small number is the treatment population below which drug development in the absence of MUMS incentives likely would not be profitable, based on a comparison of drug development costs and drug treatment values.

In the years since we first established these small numbers, drug development costs for companion animals have increased by 25 percent[13] (Ref. [3], [4]). In contrast, drug treatment values only have increased by 1 percent for dogs and have decreased by 5 percent for cats.[14] These market trends indicate that the current small numbers may exclude a subset of uncommon diseases or conditions occurring in dogs and cats with treatment populations that are too large to meet the criteria for an affirmative minor use determination and for which drug development in the absence of development incentives likely would not be profitable. This represents a market distortion that we cannot address without increasing the small numbers for dogs and cats to reflect current market conditions related to drug development costs and drug treatment values for these species.

C. Purpose of the Rule

The rule will increase the small numbers for dogs and cats in the definition of "small number of animals" to reflect current market conditions related to drug development costs and drug treatment values for purposes of determining eligibility for drug development incentives

[12] See section 102 of Public Law 108-208 (Minor Use and Minor Species Animal Health Act of 2004): https://www.govinfo.gov/content/pkg/STATUTE-118/pdf/STATUTE-118-Pg891.pdf.

[13] We base this calculation on a comparison of nominal drug development costs for companion animals in 2005 ($15 million) and 2015 ($22.5 million), converted to 2021 dollars.

[14] We base these calculations on a comparison of nominal drug treatment values for dogs and cats in 2005 ($350 and $200, respectively) and 2016 ($427 and $230, respectively), converted to 2021 dollars (see the memorandum titled "2018-2019 Reassessment of Small Numbers of Animals for Minor Use Determination" on the docket for this rulemaking).

under the MUMS Act. The small number for dogs will increase from 70,000 to 80,000, and the small number for cats will increase from 120,000 to 150,000. These increases may encourage the development of additional new animal drugs for minor uses in dogs and cats.

D. Baseline Conditions

1. History of Minor Use Determination Requests and Designations for Dogs and Cats

In Table 2, we summarize the outcomes of minor use determination requests that sponsors have submitted to us since August 2009 for dogs and cats.

Table 2. Minor Use Determination Requests and Designations for Minor Uses in Dogs and Cats

Value[a]	Dogs	Cats	Total
Minor Use Determination Requests	71	8	79
Requests with Sufficient Information	63	6	69
Requests for Minor Use Status Granted	60	4	64
Unique Minor Use Claims[b]	32	7	39
Minor Use Designations	20	0	20

[a] Values in this table apply to actions between August 26, 2009 and April 2, 2021, and are based on internal data from OMUMS.

[b] A unique minor use claim represents a unique disease or condition. Different sponsors may submit minor use determination requests for the same intended use for different drugs or dosage forms.

Since 2009, sponsors have submitted 79 requests for a determination of minor use status to us for new animal drugs for intended uses in dogs and cats. Of these requests, 69 provided enough information for us to make a definitive minor use determination. We issued an affirmative determination in 64 cases, which involved 39 unique conditions in dogs and cats. Sponsors currently submit an average of 5.9 minor use determination requests for dogs and 0.7 minor use determination requests for cats to us per year.[15]

Since August 2009, we have designated 20 MUMS drugs involving a minor use in dogs. Most of these drugs were intended to treat neoplastic conditions in dogs, including forms of leukemia, melanoma, sarcoma, lymphoma, and other cancers. We have not granted any designations for drugs intended to address conditions in cats.

2. Affected Entities

We estimate that the rule will impact 245 new animal drug sponsors. This estimate includes active sponsors of NADAs and active sponsors of abbreviated new animal drug applications (ANADAs).[16] Sponsors of ANADAs may be less likely to develop pioneer animal

[15] To calculate the average number of minor use determination requests submitted annually for dogs and cats, we divide the number of requests submitted for dogs (71) and cats (8), as shown in Table 2, by 12 years.

[16] In 2021, we estimated that 187 sponsors would be subject to user fees under ADUFA (Ref. [17]) and 60 sponsors would be subject to user fees under the Animal General Drug User Fee Act (AGDUFA) (Ref. [17]) in fiscal year 2022. To more accurately identify the number of firms that the rule will impact, we rely on an internal list of active sponsors as of April 2022. This list includes 175 ADUFA sponsors and 58 AGDUFA sponsors. After adjusting the numbers to account for those sponsors appearing under both the ADUFA and AGDUFA portions of the list, the total number of unique active sponsors as of April 2022 is 205.

drugs, and therefore less likely to submit a minor use determination request. We also include other firms that have submitted minor use determination requests since the implementation of the MUMS Act that not are currently sponsoring an NADA or ANADA.[17] We utilize proprietary data from the Dun & Bradstreet database to identify and exclude inactive firms from the final count of sponsors.

3. Assumptions Regarding the Timing of Actions from the Rule

To formulate our benefit and cost estimates, we make several simplifying assumptions regarding the timing of actions from the rule. We base these assumptions on input from FDA subject matter experts as well as data maintained by FDA regarding MUMS designations and approvals between August 26, 2009, and April 2, 2021 (Ref. [5]).

For the purposes of our benefit and cost estimates, we assume that beginning in the first year the direct final rule takes effect (year 1), sponsors will submit between 0 and 2 additional minor use determination requests to us each year, and that we will grant minor use status in all cases. We also assume that each submitted request will result in a designation in the same year.[18] Therefore, we assume that we will grant between 0 and 2 additional minor use designations each year, beginning in year 1.

We require sponsors to submit an annual progress report to us for each designated MUMS drug until we approve the drug or terminate the designation, and sponsors must submit their first progress report within 14 months after the date designation is granted.[19] OMUMS estimates that a reasonable timespan between the designation and approval of a new animal drug for a minor use in dogs or cats is 8 years. Therefore, we assume that sponsors will submit an annual progress report to us for each designated MUMS drug for a period of 7 years.

Based on our records, we observe that 30 percent of the minor use designations we have granted have resulted in a conditional or full approval of the drug within 8 years. We therefore assume that we will approve 30 percent of designated minor use drugs resulting from the rule in the ninth year of development. This means that we will expect to grant between 0 and 0.6[20] additional approvals per year for new animal drugs intended to treat minor use indications in dogs or cats, beginning in year 9.

To capture the full range of potential benefits from the rule we assume that the sponsors of these minor use drugs will apply for conditional approval before pursuing full approval. By applying for conditional approval first, sponsors are able to defer some costs of effectiveness testing until later in the drug development process, thereby decreasing their overall costs. Sponsors that do not opt for conditional approval would not realize these cost savings. Additionally, sponsors receiving conditional approval are able to legally market their drug before

[17] As of April 2022, 94 unique new animal drug sponsors have submitted a minor use determination request to OMUMS.

[18] In practice, some sponsors do not apply for designation status for their MUMS drug until later in the development process or do not pursue designation status. Sponsors are able to request designation at any time in the drug development process prior to submitting an application for either conditional or full approval of the MUMS drug. See 21 CFR 516.23.

[19] See 21 CFR 516.30.

[20] To estimate these values, we multiply our range of estimates for the annual number of minor use designations resulting from the rule (0 and 2) by 30 percent.

compiling all of the evidence needed to meet the effectiveness standard for full approval of the drug. This allows benefits to pet owners from the development of new animal drugs to begin to accrue earlier in time.

In addition, we assume that if we do not update the small numbers, those sponsors that will develop minor use drugs as a result of the rule would instead pursue alternative drug development projects through the standard NADA process. Elsewhere in this document, when we refer to what would happen "under baseline conditions" or "in the baseline," we are referring to this assumption.

We summarize our assumptions regarding the timing of actions resulting from the rule in Table 3.

Table 3. Assumptions Regarding the Timing of Actions from the Rule

Action	Low Estimate	Primary Estimate	High Estimate	Timing of Initial Action
Additional Determination Requests Submitted by Industry per Year	0	1	2	Year 1
Additional Designations Granted by FDA per Year	0	1	2	Year 1
Additional CNADAs Approved by FDA per Year	0	0.3	0.6	Year 9

E. Benefits of the Rule

1. Benefits to Pet Owners from the Development of New Animal Drugs

The rule may stimulate the development of new animal drugs for uncommon diseases or conditions in dogs and cats. This, in turn, may result in increased revenue to the sponsors of these new animal drugs, which would represent a transfer from pet owners to industry. Pet owners would benefit from the availability of new animal drugs to treat dogs and cats. We quantify this benefit to pet owners in this section.

Based on responses to a recent survey by the American Veterinary Medical Association (AVMA), 85 percent of dog owners and 76 percent of cat owners view their pet as a member of the family rather than as a companion or as property under their care (Ref. [6]). This evidence of strong bonds between dogs and cats and their owners suggests that pet owners will value any reductions in morbidity or mortality in dogs and cats with uncommon diseases or conditions.

As we state in section II.D.3, we assume that if we do not update the small numbers, those sponsors that will develop minor use drugs as a result of the rule would instead pursue alternative drug development projects through the standard NADA process, which may also benefit animal health. We do not know with certainty how pet owners' valuation of drugs resulting from these alternative drug development projects would compare to their valuation of minor use drugs resulting from the rule. We therefore assume that pet owners would value the resulting drugs equally, but that benefits to pet owners would begin to accrue earlier with the rule due to the conditional approval provisions of the MUMS Act, which allows sponsors to begin

legally marketing a conditionally approved new animal drug before compiling all of the evidence needed to meet the effectiveness standard for full approval of the drug.[21]

Sponsors can market a conditionally approved new animal drug for up to 5 years while gathering the remaining data needed to demonstrate substantial evidence of effectiveness to support full approval. In contrast, under the standard NADA process, sponsors must demonstrate substantial evidence of effectiveness (SEE) to FDA before they can market their new animal drug. Because the sponsor needs only demonstrate a reasonable expectation of effectiveness to receive conditional approval, the conditional approval pathway facilitates the earlier introduction of new animal drugs to the market. We assume that sponsors that pursue conditional approval can market their new animal drugs 3 years earlier than sponsors that only submit an NADA for full approval. We vary our assumption regarding the impact of conditional approval on time to market as part of our uncertainty and sensitivity analysis in section II.I.

As we show in Table 4, we assume that we will conditionally approve between 0 to 0.6 additional new animal drugs per year for minor use indications in dogs or cats, beginning in year 9 as a result of the rule. We also assume that these new animal drugs will treat diseases or conditions affecting from 70,000 to 80,000 dogs or from 120,000 to 150,000 cats. These ranges represent the increases in the small numbers for dogs and cats. We also assume that the rule will not impact the development of MUMS drugs for diseases or conditions affecting smaller treatment populations because they already qualify for MUMS incentives based on the current small numbers.

When calculating the small numbers for dogs and cats as part of our current reassessment of the "small number of animals" definition in 21 CFR 516.3, we assume that the nontreatment rate is 50 percent (Ref. [1]). We therefore expect that from 35,000 to 40,000 dogs per year will receive treatment with each new animal drug for a disease or condition affecting from 70,000 to 80,000 dogs. Similarly, we expect that from 60,000 to 75,000 cats per year will receive treatment with each new animal drug for a disease or condition affecting from 120,000 to 150,000 cats. This implies that the annual target treatment population for an approved MUMS drug resulting from the rule will range from 35,000 to 75,000 dogs or cats (the minimum and maximum of these ranges).

A 2018 report from Brakke Consulting Inc. (BCI) contains a sample timeframe for the commercial development of a new animal drug and estimates that an approved new animal drug reaches its annual sales target in the tenth year of marketing. We therefore conclude that an approved new animal drug reaches its annual target treatment population in its tenth year of marketing.[22]

Based on a recent AVMA survey, veterinary clients spent an average of $141 per visit for cats and $168 per visit for dogs in 2016 (Ref. [6]). We use these costs as a proxy for the value of

[21] See section 571 of the FD&C Act (21 U.S.C. 360ccc).

[22] We assume a linear increase in the treated population between the first and tenth year of marketing. In the first year of marketing, we assume that one-tenth of the target treatment population will receive treatment from an approved minor use drug. In the second year of marketing, we assume that two-tenths of the target treatment population will receive treatment. We assume that the treated population will continue to increase by one-tenth of the target treatment population each year, until the tenth year of marketing. We assume that beginning in the tenth year of marketing, 100 percent of the target treatment population will receive treatment.

pet health improvements to pet owners. We assume that, in 2021 dollars, pet owners would be willing to pay between $158 and $188 to treat a sick dog or cat with an approved animal drug resulting from the rule.

Given our assumptions, in Table 4 we compare our primary estimates of the stream of benefits to pet owners over a period of 20 years from the development of new animal drugs based on eligibility for conditional approval under the MUMS Act. We expect that any new animal drug that results from the rule will enter the market 3 years earlier than any alternative new animal drug that the same sponsors would produce in the baseline. We calculate the marginal benefits in each year by subtracting the benefits associated with a late market entry from the benefits associated with an early market entry.

Table 4. Stream of Benefits to Pet Owners from the Development of New Animal Drugs over 20 Years ($ millions)

Year	Benefits, Early Market Entry	Benefits, Late Market Entry	Marginal Benefits[a]
0–8	$0.00	$0.00	$0.00
9	$0.42	$0.00	$0.42
10	$1.27	$0.00	$1.27
11	$2.54	$0.00	$2.54
12	$4.24	$0.42	$3.81
13	$6.36	$1.27	$5.08
14	$8.90	$2.54	$6.36
15	$11.86	$4.24	$7.63
16	$15.25	$6.36	$8.90
17	$19.07	$8.90	$10.17
18	$23.30	$11.86	$11.44
19	$27.54	$15.25	$12.29

[a] Marginal benefits in each year represent the difference in benefits for the "early market entry" and "late market entry" scenarios.

We present the annualized benefits to pet owners in Table 5. We estimate that the marginal annualized benefits to pet owners from new animal drug development over 20 years will range from $0 to $4.26 million at a 7 percent discount rate, with a primary estimate of $2.13 million, and from $0 to $5.71 million at a 3 percent discount rate, with a primary estimate of $2.86 million.

Table 5. Annualized Benefits to Pet Owners from the Development of New Animal Drugs over 20 Years ($ millions)

	Primary (7%)	Low (7%)	High (7%)	Primary (3%)	Low (3%)	High (3%)
Benefits, Early Market Entry	$3.53	$0.00	$7.07	$4.85	$0.00	$9.70
Benefits, Late Market Entry	$1.41	$0.00	$2.81	$2.00	$0.00	$3.99
Marginal Benefits[a]	$2.13	$0.00	$4.26	$2.86	$0.00	$5.71

[a] These estimates represent the difference in benefits for the "early market entry" and "late market entry" scenarios.

For several reasons, we consider these to be lower bound estimates of the benefits to pet owners from the development of new animal drugs resulting from the rule. First, it is likely that pet owners choosing to treat their cat or dog with a minor use drug resulting from the increase in

small numbers will value these drugs more highly than the alternative projects that sponsors might pursue in the baseline. In the baseline, this minor use drug would not be available to treat their pet's disease or condition because the availability the drug is contingent on increasing the small numbers. Second, our reliance on the average cost of veterinary visits to value pet health improvements to pet owners may also undervalue pet owners' willingness to pay to treat a dog or cat with an uncommon disease or condition.

Most veterinary visits for dogs and cats are for preventive care and vaccinations,[23] rather than for an illness or injury[24] that requires drug treatment (Ref. [6]). Veterinary costs also do not account for the ancillary costs that pet owners may bear to treat a sick pet. These could take the form of travel costs, lost wages, and any other costs to pet owners associated with visiting a veterinarian to obtain treatment for a pet or administering a prescribed drug. Therefore, we calculate these benefits using higher willingness to pay assumptions as part of our uncertainty and sensitivity analysis in section II.I.

2. Cost Savings to Industry from Delayed Completion of Effectiveness Testing

Under the conditional approval provisions of the MUMS Act, a sponsor can market a new animal drug that has been shown to be safe and for which there is a reasonable expectation of effectiveness for up to 5 years.[25] The sponsor of the conditionally approved drug has until 4.5 years from the date the product received conditional approval to submit SEE in support of an application for full approval to FDA. We therefore assume that there will be cost savings to sponsors that seek and attain conditional approval as a result of the rule and choose to delay completion of effectiveness testing and the submission of SEE for as long as possible. In order to capture the full range of these potential cost savings to industry, we assume that in the baseline, the same sponsors would pursue development of alternative drugs that would not qualify for conditional approval. We estimate their magnitude by comparing the annualized costs of completing effectiveness testing and submitting SEE in each scenario.

Based on an estimate included in a 2005 report from BCI, demonstrating SEE accounts for on average 31 percent of the sponsor's total cost to develop a new animal drug (Ref. [3]). Additional data compiled by BCI indicate the total cost to the sponsor to develop a new animal drug for a companion animal species in 2015 was on average $22.5 million (Ref. [4]). In 2021 dollars, this number corresponds to $25.5 million. We therefore assume that sponsors spend 31 percent of $25.5 million, or approximately $7.90 million, to complete effectiveness testing and submit SEE to FDA for a single new animal drug during the development process.

To maintain consistency with our assumptions in Table 4, we assume that sponsors will spread this $7.90 million cost over the first 8 years of drug development when pursuing projects that are not eligible for conditional approval in the baseline ("early completion of testing" scenario) and spread this cost over the 5 years following conditional approval for any minor use drugs resulting from the rule ("late completion of testing" scenario). Our discounting formula

[23] In 2016, 46 percent of veterinary visits for dogs and 43 percent of visits for cats were for preventative care; 28 percent of veterinary visits for dogs and 21 percent of visits for cats were for vaccinations.
[24] In 2016, 14 percent of veterinary visits for dogs and 18 percent of visits for cats were for illness; 5 percent of veterinary visits for dogs and 4 percent of visits for cats were for injury.
[25] We assume that the cost to sponsors of showing reasonable expectation of effectiveness in support of conditional approval would be negligible.

assumes that costs are incurred at the beginning of each year. Therefore, our assumption for the late completion of testing scenario is consistent with the maximum amount of time a sponsor of a conditionally approved drug has to submit SEE to FDA in support of their application for full approval of the drug (4.5 years).

It is possible that sponsors will conduct effectiveness testing or submit SEE, or both, for new animal drugs that we ultimately will not approve. For simplicity, in this quantification of cost savings, we only consider costs for those new animal drugs that we ultimately will approve. We show our primary estimate of the stream of cost savings to industry[26] in Table 6.

Table 6. Stream of Cost Savings to Industry from Delayed Completion of Effectiveness Testing over 20 Years ($ millions)

Year	Costs, Early Completion of Testing	Costs, Late Completion of Testing	Cost Savings[a]
0	$0.00	$0.00	$0.00
1	$0.30	$0.00	$0.30
2	$0.59	$0.00	$0.59
3	$0.89	$0.00	$0.89
4	$1.18	$0.00	$1.18
5	$1.48	$0.00	$1.48
6	$1.78	$0.00	$1.78
7	$2.07	$0.00	$2.07
8	$2.37	$0.00	$2.37
9	$2.37	$0.47	$1.90
10	$2.37	$0.95	$1.42
11	$2.37	$1.42	$0.95
12	$2.37	$1.90	$0.47
13–19	$2.37	$2.37	$0.00

[a] Cost savings in each year represent the difference in costs for the "early completion of testing" and "late completion of testing" scenarios.

The annualized cost savings to industry from delayed completion of effectiveness testing by sponsors that seek and attain conditional approval as a result of the rule, which we present in Table 7, will range from $0 to $1.72 million at a 7 percent discount rate, with a primary estimate

[26] For the "late completion of testing" scenario, we estimate that 0 to 0.6 sponsors will incur costs related to effectiveness testing and the submission of SEE in year 9 for conditional approvals occurring in year 9. In year 10, we estimate that 0 to 0.6 sponsors will incur costs for conditional approvals occurring in year 9 and 0 to 0.6 sponsors will incur costs for conditional approvals occurring in year 10 (or 0 to 1.2 sponsors in total). In addition, we estimate that beginning in year 13, 0 to 0.6 sponsors will incur costs for conditional approvals in years 9 through 13, respectively (or 0 to 3 sponsors in total). In year 13, sponsors will incur their final costs related to effectiveness testing and the submission of SEE for conditional approvals occurring in year 9. This represents the maximum number of sponsors that will collectively incur costs related to effectiveness testing and the submission of SEE for conditional approvals resulting from the rule in a given year. We apply similar logic to develop the stream of costs for the "early completion of testing" scenario.

of $0.86 million, and from $0 to $1.64 million at a 3 percent discount rate, with a primary estimate of $0.82 million.

Table 7. Annualized Cost Savings to Industry from Delayed Completion of Effectiveness Testing over 20 Years ($ millions)

	Primary (7%)	Low (7%)	High (7%)	Primary (3%)	Low (3%)	High (3%)
Costs, Early Completion of Testing	$1.56	$0.00	$3.12	$1.72	$0.00	$3.44
Costs, Late Completion of Testing	$0.70	$0.00	$1.40	$0.90	$0.00	$1.80
Cost Savings[a]	$0.86	$0.00	$1.72	$0.82	$0.00	$1.64

[a] These estimates represent the difference in costs for the "early completion of testing" and "late completion of testing" scenarios.

3. Cost Savings to FDA from Delayed Completion of SEE Review

We likewise assume that there will be cost savings to FDA related to the delayed completion of reviewing SEE from sponsors that seek and attain conditional approval as a result of the rule. To determine the magnitude of these cost savings, we first estimate the cost to FDA to review SEE for a new animal drug based on (1) the time it takes us to review SEE for a new animal drug and (2) the fully-loaded hourly wage for CVM employees.

We estimate the time it takes us to review SEE for a new animal drug based on the time it takes us to review an NADA and a CNADA. Since we do not have data on the paperwork burden for us to review NADAs or CNADAs, we estimate these values based on the paperwork burden for us to review ANADAs. We assume, based on CVM's time reporting system, that it takes us four times longer to review an NADA than an ANADA. In addition, based on input from FDA's subject matter experts, we assume that the time it takes to review a CNADA equals the time to review an NADA. In a 2016 supporting statement for ANADAs (OMB Control No. 0910-0669), we reported that FDA spent 47,415 hours to review 21 ANADAs (Ref. [7]). We therefore assume that it takes FDA 2,258[27] hours to review a single ANADA and 9,031[28] hours to review a single NADA or CNADA. Consistent with the estimate from BCI that demonstrating SEE accounts for 31 percent of the cost of drug development to industry, we assume that reviewing SEE constitutes 31 percent of FDA's time burden to review an NADA or CNADA (2,800 hours) (Ref. [3]). We use 2021 data on FDA fully-loaded[29] Full Time Equivalent (FTE) costs to estimate the fully-loaded hourly wage for CVM employees ($137.71).

Given these assumptions, we assume the total cost to FDA to review SEE for a new animal drug equals $0.39 million.[30] We also assume that FDA will incur this $0.39 million cost over the 5 years following conditional approval for any minor use drugs resulting from the rule ("late completion of SEE review" scenario) and incur these cost over the first 8 years of drug

[27] We divide 47,415 hours by 21 ANADAs.
[28] We multiply 2,258 by 4.
[29] The "fully-loaded" wage represents the full burden of an employee's time to the employer. It equals the base wage plus benefits and other overhead costs.
[30] We multiply 2,800 hours by $137.71.

development to review SEE for the same sponsors in the baseline ("early completion of SEE review" scenario). We display our primary estimate of the stream of cost savings to FDA in Table 8.

Table 8. Stream of Cost Savings to FDA from Delayed Completion of SEE Review over 20 Years

Year	Costs, Early Completion of SEE Review	Costs, Late Completion of SEE Review	Cost Savings[a]
0	$0.00	$0.00	$0.00
1	$0.01	$0.00	$0.01
2	$0.03	$0.00	$0.03
3	$0.04	$0.00	$0.04
4	$0.06	$0.00	$0.06
5	$0.07	$0.00	$0.07
6	$0.09	$0.00	$0.09
7	$0.10	$0.00	$0.10
8	$0.12	$0.00	$0.12
9	$0.12	$0.02	$0.09
10	$0.12	$0.05	$0.07
11	$0.12	$0.07	$0.05
12	$0.12	$0.09	$0.02
13–19	$0.12	$0.12	$0.00

[a] Cost savings in each year represent the difference in costs for the "early completion of SEE review" and "late completion of SEE review" scenarios.

In Table 9, we show that the annualized cost savings to FDA from delayed completion of reviewing SEE will range from $0 to $83,955 at a 7 percent discount rate, with a primary estimate of $41,977, and from $0 to $80,028 at a 3 percent discount rate, with a primary estimate of $40,014.

Table 9. Annualized Cost Savings to FDA from Delayed Completion of SEE Review over 20 Years ($ millions)

	Primary (7%)	Low (7%)	High (7%)	Primary (3%)	Low (3%)	High (3%)
Costs, Early Completion of SEE Review	$0.08	$0.00	$0.15	$0.08	$0.00	$0.17
Costs, Late Completion of SEE Review	$0.03	$0.00	$0.07	$0.04	$0.00	$0.09
Cost Savings[a]	$0.04	$0.00	$0.08	$0.04	$0.00	$0.08

[a] These estimates represent the difference in costs for the "early completion of SEE review" and "late completion of SEE review" scenarios.

F. Costs of the Rule

1. Costs to Industry to Read and Understand the Rule

We expect that the 245 new animal drug sponsors identified in section II.D.2 will incur a one-time cost to read and understand the rule in year 0. We assume that 1 to 3 employees from each entity will read the rule's preamble and codified language and the related memorandum,

which contain approximately 11,000 words in total. We also assume that each reviewer will read at the average adult reading speed of 200 words to 250 words per minute. Based on these assumptions, it will take each reviewer between 44 minutes and 55 minutes to read the rule and its related memorandum. Given the simplicity of the codified language, we do not expect that reviewers will need additional time to understand the rule.

To value the time for sponsors to read and understand the rule, we use composite wages calculated from the Bureau of Labor Statistics' (BLS) National Industry-Specific Occupational Employment and Wage Estimates for the pharmaceutical and medicine manufacturing industry (NAICS 325400) in May 2021 (Ref. [8]). We assume a reviewer mix for each sponsor of 50 percent medical and health services managers (occupation code 11-9111) and 50 percent lawyers (occupation code 23-1011). This mix yields a composite wage of $95.69.[31] We double this wage to account for employee benefits and overhead, yielding a fully-loaded hourly wage of $191.38 per reviewer.

We estimate that the cost per reviewer to read and understand the rule will range from $140 to $175 and that total review costs per entity will range from $140 to $526. We assume that there are currently 245 active new animal drug sponsors. Therefore, we estimate that the total costs for reading and understanding the rule will range from $34,385 to $128,942.[32] Over 20 years, annualized costs will range from $3,033 to $11,375 at a 7 percent discount rate, with a primary estimate of $7,204, and from $2,244 to $8,415 at a 3 percent discount rate, with a primary estimate of $5,329.

2. Costs to Industry to Prepare and Submit Minor Use Determination Requests

The rule may stimulate the development of new animal drugs to treat uncommon diseases or conditions in dogs and cats by increasing the small number for each of these species. This change may make more new animal drugs under consideration by sponsors eligible for minor use status, and in turn, MUMS development incentives. As we show in Table 4 in section II.E.1, we assume that sponsors will submit between 0 and 2 additional minor use determination requests per year in total, with a primary estimate of 1 request. Based on the estimated annual reporting burden included in the final rule we published in July 2007 ("Designation of New Animal Drugs for Minor Uses or Minor Species") to implement the designation provisions of the FD&C Act, we assume that it takes managers 16 hours[33] on average to prepare and submit a single minor use determination request to FDA (Ref. [9]). Based on BLS' National Industry-Specific Occupational Employment and Wage Estimates for medical and health services managers in the pharmaceutical and medicine manufacturing industry in May 2021, the fully-loaded wage rate for these employees is $196.52 (Ref. [8]).

Given these assumptions, we estimate that annual costs to industry to prepare and submit minor use determination requests for additional new animal drugs will range from $0 to $6,289, with a primary estimate of $3,144. We also assume that these costs will begin to accrue in year 1. Based on these estimates and assumptions, the annualized costs over 20 years will range from $0

[31] The hourly wage for medical and health services managers is $98.26, and the hourly wage for lawyers is $93.12.
[32] These values equal $140.35 × 245 and $526.30 × 245, respectively.
[33] We assume that the level of effort for preparing and submitting a minor use determination request includes the level of effort for preparing and submitting a designation request.

to $5,734 at a 7 percent discount rate, with a primary estimate of $2,867, and from $0 to $5,878 at a 3 percent discount rate, with a primary estimate of $2,939.

3. Costs to FDA to Review Minor Use Determination Requests

We estimate that it takes us 16 hours[34] on average to review each request for a minor use determination and issue a determination to the sponsor (or, alternatively, to notify the sponsor that they have provided insufficient information to support a determination). Adopting the fully-loaded hourly wage for CVM employees in 2021, we estimate that additional annual costs to FDA to review minor use determination requests will range from $0 to $4,407, with a primary estimate of $2,203. We assume that these costs will begin to accrue in year 1. Based on these estimates and assumptions, the annualized costs over 20 years will range from $0 to $4,018 at a 7 percent discount rate, with a primary estimate of $2,009, and from $0 to $4,119 at a 3 percent discount rate, with a primary estimate of $2,060.

4. Costs to Industry to Prepare and Submit Annual Designation Reports

As we show in Table 4 in section II.E.1, we assume that we will grant between 0 and 2 additional minor use designations per year beginning in year 1. We require sponsors of all designated new animal drugs to submit annual progress reports to us until we either terminate the designation or we conditionally or fully approve the designated new animal drug.[35] We assume that sponsors of designated new animal drugs will begin submitting reports to OMUMS in the year following the initial designation. Therefore, we expect that reporting costs to industry will begin to accrue in year 2.

We further assume, based on our July 2007 final rule ("Designation of New Animal Drugs for Minor Uses or Minor Species"), that it takes medical and health services managers 2 hours to prepare and submit each report, for a cost of $393[36] per annual report (Ref. [9]). Therefore, in the first year of reporting, total industry reporting costs will range from $0 to $786. We assume that each sponsor will submit an annual designation report for a period of 7 years since they will submit their first report in the year following designation. This means that total industry reporting costs will increase over time until year 8.[37] Following year 8, estimated annual costs to industry from reporting will remain constant over time.

We present the stream of costs to industry to prepare additional annual designation reports over 20 years in Table 10. The annualized costs over 20 years, which are derived from

[34] We assume that the level of effort for reviewing a minor use determination request (16 hours) includes the level of effort for reviewing a designation request.
[35] See 21 CFR 516.30.
[36] We use the fully-loaded hourly wage for medical and health services managers in the pharmaceutical and medicine manufacturing industry ($196.52) in this calculation.
[37] Based on our assumption that each sponsor will submit an annual designation report for a period of 7 year, we estimate that in year 2, sponsors will submit 0 to 2 designation reports resulting from designation requests in year 1. In year 3, sponsors will submit 0 to 2 reports resulting from requests in year 1 and 0 to 2 reports resulting requests in year 2 (or 0 to 4 reports in total). Beginning in year 8, sponsors will submit 0 to 2 reports resulting from requests in years 1 through 7, respectively (or 0 to 14 reports in total). Sponsors will submit their final reports for designations resulting from year 1 designation requests in year 8. This represents the maximum number of designation reports that sponsors will collectively submit to us in a given year for designations resulting from the rule.

Table 10, will range from $0 to $3,421 at a 7 percent discount rate, with a primary estimate of $1,711, and from $0 to $3,827 at a 3 percent discount rate, with a primary estimate of $1,914.

Table 10. Stream of Costs to Industry to Prepare Annual Designation Reports over 20 Years ($)

Year	Primary Estimate	Low Estimate	High Estimate
0–2	$393	$0	$786
3	$786	$0	$1,572
4	$1,179	$0	$2,358
5	$1,572	$0	$3,144
6	$1,965	$0	$3,930
7	$2,358	$0	$4,716
8–19	$2,751	$0	$5,503

5. Costs to FDA to Review Annual Designation Reports

We may incur costs to review additional annual reports for designated minor use drugs resulting from the rule. FDA estimates that it takes a reviewer 6 hours to review a single report. Using the fully-loaded hourly wage for CVM employees in 2021, this amounts to $826 per annual report. Assuming that each sponsor will submit an annual designation report for a period of 7 years, expected costs in year 2 will range from $0 to $1,652. These costs will increase annually until year 8. We assume annual costs to us for reviewing designation reports will remain constant following year 8.

Given these assumptions, we display the stream of costs to FDA to review additional annual designation reports over 20 years in Table 11. The annualized costs over 20 years, which are derived from Table 11, will range from $0 to $7,192 at a 7 percent discount rate, with a primary estimate of $3,596. Annualized costs at a 3 percent discount rate will range from $0 to $8,046, with a primary estimate of $4,023.

Table 11. Stream of Costs to FDA to Review Annual Designation Reports over 20 Years ($)

Year	Primary Estimate	Low Estimate	High Estimate
0–2	$826	$0	$1,652
3	$1,652	$0	$3,305
4	$2,479	$0	$4,957
5	$3,305	$0	$6,610
6	$4,131	$0	$8,262
7	$4,957	$0	$9,915
8–19	$5,784	$0	$11,567

6. Potential Administrative Time Costs to Industry and FDA Related to the MUMS Program

Industry and FDA may incur additional administrative time costs associated with conditional approval as a result of the rule. These may include costs to industry to prepare and submit additional predevelopment plans for CNADAs and annual requests for renewal of conditional approval for conditionally approved new animal drugs resulting from the rule. FDA will incur costs to review any predevelopment plans and requests for renewal of conditional

approval submitted by industry. We assume that these costs will be negligible based on input from FDA subject matter experts.

There may also be administrative time costs to industry and FDA involving increased quantities of amendments to minor use designations, transfers of sponsorship for minor use designations, sponsors' responses to FDA notifications, and other correspondences between sponsors and FDA related to the MUMS program. Industry may also bear costs to prepare and submit additional requests for waivers from user fees under the MUMS waiver provision, as well as additional applications for grants to support safety and effectiveness testing. FDA will incur costs to review any submitted user fee waiver requests and grant applications from industry.

G. Distributional Effects

1. User Fee Waivers

We assume that additional sponsors may apply for and receive user fee waivers from us as a result of the rule. This will result in within-industry transfers to these sponsors from fee-paying sponsors.

For our low estimate of these transfers, we assume that no sponsors that will develop a new animal drug for a minor use in dogs or cats as a result of the rule will receive user fee waivers. For our high estimate of these transfers, we assume that all of these sponsors will receive user fee waivers. In this high estimate, we assume that each sponsor will receive a one-time application fee waiver and begin receiving annual establishment and product fee waivers in the year we approve their new animal drug. They also will receive annual sponsor fee waivers beginning in the first year of development of their new animal drug. We summarize these assumptions in Table 12.

Table 12. Summary of Assumptions Regarding User Fees by Type

User Fee Type	Frequency of User Fee	Time of Onset of User Fee	Waiver Recipients (Low Estimate)	Waiver Recipients (High Estimate)
Application[a]	One-time	Year of approval	No sponsors	All sponsors
Establishment	Annual	Year of approval	No sponsors	All sponsors
Product	Annual	Year of approval	No sponsors	All sponsors
Sponsor	Annual	First year of development	No sponsors	All sponsors

[a] We assume that all sponsors that will develop a new minor use drug as a result of the rule will be subject to the full (rather than supplemental) application fee in the absence of a waiver.

We apply ADUFA user fee rates for fiscal year 2022 to estimate the magnitude of within-industry transfers resulting from user fee waivers.[38] It is possible that sponsors will apply for user fee waivers for new animal drugs that we ultimately will not approve. For simplicity, in this quantification of transfers, we only consider waivers for those new animal drugs that we will ultimately approve. The annualized value of transfers will range from $0 to $0.94 million at a 7

[38] For fiscal year 2022, the full application fee is $580,569, the establishment fee is $155,220, the product fee is $10,787, and the sponsor fee is $137,791 (Ref. [17]).

percent discount rate, with a primary estimate of $0.47 million, and from $0 to $1.14 million at a 3 percent discount rate, with a primary estimate of $0.57 million.

2. Grants

We assume that sponsors that will choose to develop a new animal drug for a minor use in dogs or cats as a result of the rule may apply for and receive grants from us to support safety and effectiveness testing for their product. This would result in transfers from government to industry.

For our low estimate of these transfers, we assume that no eligible sponsors will apply for grants. For our high estimate of these transfers, we assume that all eligible sponsors will apply for and receive grant funding at a total value of $750,000 during the drug development process. We further assume that sponsors will spread this funding over the first 8 years of drug development and the first 3 years of conditional approval (i.e., over 11 years). As we show in Table 4 in section II.E.1, we assume that we will designate between 0 and 2 new animal drugs per year, beginning in year 1. Therefore, we expect to issue between $0 to $136,364[39] in grant funding in year 1. These transfers will increase annually until year 11. We assume annual transfers in the form of grants to support safety and effectiveness testing will remain constant following year 11 at a range of $0 to $1.5 million[40] per year.

Based on these assumptions, the annualized value of transfers from government to industry will range from $0 to $0.86 million at a 7 percent discount rate, with a primary estimate of $0.43 million, and from $0 to $0.97 million at a 3 percent discount rate, with a primary estimate of $0.48 million.

3. Exclusive Marketing Rights

Any designated minor use drugs that FDA approves or conditionally approves as a result of the rule will receive 7 years of exclusive marketing rights. These exclusive marketing rights grant protection from other animal drug sponsors seeking approval for the same drug, dosage form, and intended use, and provide additional years of protection compared to drugs that have not been designated.

Total surplus from a new animal drug equals the sum of consumer and producer surplus. Consumer surplus equals the difference between what consumers are willing to pay for the drug and the market price. Producer surplus equals the difference between the revenue sponsors receive from marketing the drug and their cost of production. Holding all else equal, granting a new animal drug additional years of marketing protections delays the approval of lower-priced generic copies and competing pioneers. In practice, this means that the rights holder can remain the sole producer (monopolist) and sell their new animal drug at a higher price for a longer period of time. This results in:

1. A transfer of producer surplus to the sole producer from would-be producers of generic copies and producers of competing pioneers;

[39] This value equals 2 designations × $750,000 in grant funding ÷ 11 years, respectively.
[40] This value equals $136,364 × 11 years, respectively.

2. A transfer of surplus from consumers to the sole producer (in the form of higher profits); and
3. A cost in the form of forgone producer and consumer surplus resulting from the market inefficiencies of the monopoly (known as "deadweight loss").[41]

However, as we argue in sections II.D.3 and II.E.1, increasing the small numbers for dogs and cats may result in the approval of a different mix of new animal drugs which may enter the market earlier (violating the "holding all else equal" condition). This would result in the creation of new markets for these drugs which may, in turn, increase total surplus by more than the deadweight loss resulting from the additional marketing protections. Due to uncertainty in how supply and demand for these drugs would compare to supply and demand for the drugs produced under baseline conditions, the impact of 7 years of exclusive marketing rights for these drugs on total surplus is similarly uncertain.

4. Other Distributional Effects of the Rule

The rule may bring to the market new drug treatment options for uncommon diseases or conditions occurring in dogs and cats. Depending on the type of new animal drugs that sponsors produce, this could result in transfers between sponsors of substitutable drugs. For example, if a sponsor develops a new animal drug that effectively treats an uncommon neoplastic condition in dogs as a result of the rule, this could lead to increased revenue to the sponsor of the new animal drug and decreased revenue to sponsors of palliative drugs that alleviate symptoms of the disease in the absence of an effective treatment.

A new animal drug that a sponsor develops in response to the rule may be more expensive than existing treatment options, may be purchased by veterinarians or pet owners to treat dogs or cats at a higher rate, or may enter the market earlier than the alternative projects that sponsors would pursue under baseline conditions. In these cases, we additionally expect transfers from pet owners or veterinarians, or both, to sponsors in the form of increased revenue.

H. International Effects

We assume that this rule will affect all potential sponsors of new animal drugs marketed in the United States no matter where the sponsors are located. Our analysis estimates the impacts of this rule on all such entities.

I. Uncertainty and Sensitivity Analysis

1. Benefits to Pet Owners from the Development of New Animal Drugs under Uncertainty

[41] The magnitude of the deadweight loss depends on the price elasticity of demand for the new animal drug (the responsiveness of quantity demanded in relation to changes in price). If demand for the new animal drug is relatively inelastic (not responsive to changes in price), the deadweight loss will be minimal.

Using the cost of veterinary visits to pet owners as a proxy for the value of pet health improvements, as we do in section II.E.1, may underestimate the benefits to pet owners from the development of new animal drugs as a result of the rule. In this section, we re-estimate these benefits using higher willingness to pay assumptions.

To formulate these assumptions, we adopt Carlson et al.'s methodology for estimating the value of a statistical life year (VSLY) for a dog. In a recent study in the *Journal of Benefit Cost Analysis*, Carlson et al. model the VSLY for a dog by asking owners how much they would be willing to pay for a hypothetical vaccine that reduces their dog's risk of contracting a new strain of canine influenza (Ref. [10]). Descriptive results from the paper allow us to estimate this value based on dog age and life expectancy; whether the respondent views their dog as a companion; and whether the respondent is receptive to the hypothetical scenario. Since we are not aware of any similar VSLY estimates for cats, we use this model to estimate the VSLY for a representative dog *or* cat that may receive treatment with an approved drug resulting from the rule.

To estimate the VSLY for a dog or cat that may receive treatment with a new minor use drug, we adopt a life expectancy of approximately 13 years[42] (based on an internet search) and use the median of this life expectancy (approximately 7 years) to represent pet age at time of treatment. We additionally include Carlson et al.'s companionship and receptivity corrections. Based on these assumptions, we estimate a VSLY of $2,386 when discounting future life years by 7 percent and a VSLY of $1,983 when discounting future life years by 3 percent. After converting these values from 2019 to 2021 dollars, we assume that pet owners would be willing to pay $2,518 at 7 percent discount rate and $2,093 at a 3 percent discount rate to treat a dog or cat with an approved drug resulting from the rule.

In addition to uncertainty in the degree to which pet owners would value new animal drugs that may result from the rule, there is uncertainty in the impact of conditional approval on time to market for new animal drugs. In section II.E.1, we assume that sponsors that initially pursue conditional approval can market their new animal drugs 3 years earlier than sponsors that initially submit an NADA. To assess the sensitivity of our estimates to this assumption of a 3-year marketing advantage, we estimate benefits using alternate assumptions of 1 year and 5 years.

We display the annualized benefits to pet owners from the development of new animal drugs under uncertainty in Table 13. Assuming a high willingness to pay and a 3-year marketing advantage for conditionally approved drugs, the marginal annualized benefits to pet owners from new animal drug development over 20 years will range from $0 to $56.94 million at a 7 percent discount rate, with a primary estimate of $28.47 million, and from $0 to $63.49 million at a 3 percent discount rate, with a primary estimate of $31.74 million.

[42] Based on proprietary data from the AVMA, in 2016, there were 76.8 million dogs in the United States and 58.4 million cats (Ref. [6]). An internet search suggests that the average life expectancy for a dog is 12 years and the average life expectancy for a cat is 15 years (Ref. [17]). Thus, weighting by each species' share of the national population of dogs and cats, we estimate an average life expectancy for a cat or dog of approximately 13 years (12 years × 0.57 + 15 years × 0.43).

Table 13. Annualized Benefits to Pet Owners from the Earlier Marketing of New Animal Drugs under Uncertainty over 20 Years ($ millions)

WTP Assumption	Marketing Advantage[a]	Primary (7%)	Low (7%)	High (7%)	Primary (3%)	Low (3%)	High (3%)
Low	1 Year	$0.86	$0.00	$1.72	$1.14	$0.00	$2.27
Low	5 Years	$2.90	$0.00	$5.80	$3.93	$0.00	$7.87
High	1 Year	$11.49	$0.00	$22.98	$12.63	$0.00	$25.26
High[b]	3 Years	$28.47	$0.00	$56.94	$31.74	$0.00	$63.49
High	5 Years	$34.35	$0.00	$68.70	$38.52	$0.00	$77.03

[a] We define "marketing advantage" as the number of years earlier a sponsor that initially pursues conditional approval can market their new animal drug compared to a sponsor that initially submits an NADA.
[b] We present the corresponding estimate under low willingness to pay (WTP) in Table 6.

Our high estimates likely overvalue benefits to pet owners. Not all minor use new animal drugs directly target life-threatening diseases. In addition, we assume that maximum health benefits would be achieved with one treatment; however, multiple courses of drug treatment may be required in many instances.

2. Uncertainty Regarding Baseline Assumptions

In our quantification of benefits and costs, we assume that if we do not update the small numbers, any sponsors that will develop minor use drugs as a result of the rule would instead pursue alternative drug development projects through the standard NADA process. In this section, we address two areas of uncertainty regarding our assumptions about the world without the rule (i.e., under baseline conditions): (1) whether sponsors would pursue alternative new animal drug development projects if the small numbers are not increased (we assume they would) and (2) whether those projects would qualify for FDA drug development incentives (we assume they would not).

We assume that both with and without the rule, sponsors would pursue new animal drug development projects, with the distinction that drug projects pursued with the rule will be eligible for MUMS development incentives. Under this assumption, drug development costs are not an incremental cost of the rule, because these costs would be borne by sponsors with or without the rule (with sponsors realizing cost savings under the rule due to differences in the magnitude and timing of these costs). If it is not the case that a given sponsor would reallocate resources toward other new animal drug development project(s) under baseline conditions, then we would consider the standard development costs they would incur to develop a new minor use drug with the rule (e.g., costs related to drug chemistry, manufacturing, or testing) to be incremental costs of the rule. For example, if a new company forms to develop a new minor use animal drug as a result of the rule, this would not represent a reallocation of resources under the rule.

Next, it is possible that the alternative projects that sponsors would pursue under baseline conditions would also be eligible for drug development incentives. These alternative projects could include the development of new animal drugs that already qualify for MUMS incentives based on the current small numbers or for user fee waivers under waiver provisions other than the MUMS drug waiver provision. If this is the case, then this would decrease the magnitude of estimated cost savings and transfers from the rule.

There is additionally a high degree of uncertainty regarding how pet owners will value any new minor use drugs resulting from the rule compared to the alternative projects that sponsors would pursue under baseline conditions. How pet owners will value a new minor use drug will likely vary based on the type of drugs that sponsors develop. Since August 2009, FDA has granted minor use status to new animal drugs that treat terminal and non-terminal diseases, alleviate side effects of existing medications, provide pain management, and support palliative care, among other uses in dogs and cats. For example, pet owners would likely value a minor use drug that may slow the growth of cancer cells in dogs more than a minor use drug that merely mitigates the symptoms of the same cancer, because there is greater potential for the former drug to delay mortality.

J. Analysis of Regulatory Alternatives to the Rule

1. Issue Guidance to Update the Small Numbers for Dogs and Cats

One alternative to the rule is to update the small numbers for dogs and cats through guidance instead of through regulation. However, this is not a feasible alternative. In the 2009 "Defining 'Small Number of Animals' for Minor Use Designation" final rule, we committed to periodically reevaluating and updating the "small number of animals" definition as necessary (Ref. [2]). Because the definition of "small number of animals" is codified in our regulation at 21 CFR 516.3(b), we can only update the definition by amending the regulation.

2. Maintain Status Quo

Another alternative to the rule is to maintain the current small number of animals definitions for dogs and cats. However, we expect that this would perpetuate the current market distortion resulting from inconsistencies between the existing small numbers and current drug development costs and drug treatment values (as discussed in section II.B) that we intend for the rule to mitigate.

III. Final Small Entity Analysis

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because quantified effects of the rule on sponsors are less than 0.32 percent of average annual revenues for the smallest firms, we propose to certify that this rule will not have a significant economic impact on a substantial number of small entities. This analysis, as well as other sections in this document, serves as the Final Regulatory Flexibility Analysis, as required under the Regulatory Flexibility Act.

A. Description and Number of Affected Small Entities

This rule will affect all potential sponsors of new animal drugs to treat uncommon diseases or conditions in dogs and cats in the United States, including potential sponsors that may qualify as small businesses. Sponsors are designated under the North American Industry

Classification System (NAICS) as "pharmaceutical preparation manufacturers" (NAICS 325412). The Small Business Administration (SBA) size threshold for small businesses in this category is 1,250 employees (Ref. [11]). Statistics of U.S. Businesses (SUSB) data from the U.S. Census allow us to estimate the number of small establishments using a size threshold of 1,000 employees.

SUSB data from 2018[43] indicate that 982 pharmaceutical preparation manufacturers have fewer than 1,000 employees (Ref. [12]). These data also show that there are 1,065 total firms in this industry. Using this information, we estimate that 92 percent of firms in the category are small. Proprietary data from Dun & Bradstreet indicate that 191 of the 245 active developers of animal drugs that we have identified operate domestically. Therefore, we assume that 176[44] of these entities are small.

We assume that the percentage of small drug sponsors in each employment category matches the distribution of pharmaceutical preparation manufacturers by size in 2018. We further assume that average annual receipts for these firms match average annual receipts for pharmaceutical preparation manufacturers in the corresponding size category in 2017, the most recent year for which SUSB has published receipts information (Ref. [13]).[45] We summarize these assumptions in Table 14.

Table 14. Description of Small Sponsors of New Animal Drugs

Employment Size	Number of Firms	Percent of Small Firms	Annual Receipts per Firm ($2021 m)	Total Annual Receipts ($2021 m)
0–19	110	63%	$3.39	$375.05
20–99	35	20%	$19.54	$690.29
100–299	19	11%	$58.16	$1,105.59
300–499	7	4%	$149.79	$993.98
500–999	5	3%	$201.13	$937.84
All Small	176	100%	$23.30	$4,102.76

B. Description of the Potential Impacts of the Rule on Small Entities

To calculate net costs of the rule as it relates to small firms, we consider the costs to read and understand the rule; costs to prepare and submit minor use determination requests to FDA; and costs to prepare and submit annual progress reports for active minor use designations to FDA. We also account for the value of transfers from government to sponsors in the form of grants.

We estimate that annualized net costs to industry over 20 years will range from a cost saving of $2.56 million to a cost of $3,033 at a 7 percent discount rate and from a cost saving of $2.59 million to a cost of $2,244 at a 3 percent discount rate. To estimate the average annualized net cost per firm, we divide the annualized net costs by the total number of active developers of

[43] As of August 2021, when we performed this analysis, 2018 was the most recent year for which the U.S. Census Bureau has published SUSB data on count of firms by employment size.
[44] This equals 191 × 0.92.
[45] As of August 2021, when we performed this analysis, 2017 was the most recent year for which the U.S. Census Bureau has published SUSB data on receipts by detailed employment size class.

animal drugs that we identified in section II.A (245). The average annualized net cost per firm will range from a cost saving of $10,429 to a cost of $12 at a 7 percent discount rate and from a cost saving of $10,560 to a cost of $9 at a 3 percent discount rate.

In Table 15, we present annualized net costs per firm as a percentage of average annual revenue. We base these estimates on the per firm annual receipts by size class values in Table 15. We find that quantified net costs represent less than 0.32 percent of annual revenues for all size categories of small firms.

Table 15. Annualized Net Costs per Firm as a Percentage of Average Annual Revenue

Employment Size	Low Estimate (7%)	High Estimate (7%)	Low Estimate (3%)	High Estimate (3%)
0–19	<0.001%	0.307%	<0.001%	0.311%
20–99	<0.001%	0.053%	<0.001%	0.054%
100–299	<0.001%	0.018%	<0.001%	0.018%
300–499	<0.001%	0.007%	<0.001%	0.007%
500–999	<0.001%	0.005%	<0.001%	0.005%
All Small	<0.001%	0.045%	<0.001%	0.045%

Our analysis of the impact of the rule on small entities that manufacture animal drugs and operate domestically suggests that small firms will not be significantly affected by the rule. We do not estimate the impact of the rule on other small entities, such as non-profits or state and local governments, because we do not anticipate that the rule will affect these entities. We therefore certify that this rule will not have a significant economic impact on a substantial number of small entities.

IV. References

The following references are cited in the analysis. FDA has verified the Web site addresses for the references displaying a URL, but FDA is not responsible for any subsequent changes to the Web sites after this document publishes in the Federal Register (FR).

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