■ 2. In § 14.100, add paragraph (a)(5) to read as follows:

§ 14.100 List of standing advisory committees.

* * * * *

(a) * * *

(5) *Tobacco Products Scientific Advisory Committee.*

(i) Date Established: August 12, 2009.

(ii) Function: The committee reviews and evaluates safety, dependence, and health issues relating to tobacco products and provides appropriate advice, information, and recommendations to the Commissioner of Food and Drugs. Specifically, the committee will submit reports and recommendations on tobacco-related topics, including: The impact of the use of menthol in cigarettes on the public health, including such use among children, African Americans, Hispanics and other racial and ethnic minorities; the nature and impact of the use of dissolvable tobacco products on the public health, including such use on children; the effects of the alteration of nicotine yields from tobacco products and whether there is a threshold level below which nicotine yields do not produce dependence on the tobacco product involved; and any application submitted by a manufacturer for a modified risk tobacco product. The committee may provide recommendations to the Secretary of Health and Human Services regarding any regulations to be issued under the Federal Food, Drug, and Cosmetic Act and may review any applications for new tobacco products or petitions for exemption under section 906(e) of the Family Smoking Prevention and Tobacco Control Act. The committee may consider and provide recommendations on any other matter as provided in the Family Smoking Prevention and Tobacco Control Act.

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Dated: August 19, 2009.

David Horowitz,

Assistant Commissioner for Policy.

[FR Doc. E9–20485 Filed 8–26–09; 8:45 am]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 516

[Docket No. FDA–2008–N–0176; Formerly Docket No. 2008N–0011]

RIN 0910–AG03

Defining ''Small Number of Animals'' for Minor Use Designation

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The designation provision of the Minor Use and Minor Species Animal Health Act of 2004 (MUMS Act) provides incentives to animal drug sponsors to encourage drug development and approval for minor species and for minor uses in major animal species. Congress provided a statutory definition of ''minor use'' that relied on the phrase ''small number of animals'' to characterize such use. At this time, the Food and Drug Administration (FDA) is amending the implementing regulations of the MUMS Act. In response to Congress' charge to the agency to further define minor use, this amendment establishes a specific ''small number of animals'' for each of the seven major animal species to be used in determining whether any particular intended use in a major species is a minor use.

DATES: This rule is effective November 9, 2009.

FOR FURTHER INFORMATION CONTACT: Meg Oeller, Center for Veterinary Medicine (HFV–50), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 240–276–9005, e-mail: *Margaret.Oeller@fda.hhs.gov*.

SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of March 18, 2008 (73 FR 14411), FDA issued a proposed rule (the March 2008 proposed rule) intended to define the term ''small number of animals'' for each of the seven major animal species to be used in determining whether any particular intended use in a major species is a minor use. As noted in that proposed rule, the MUMS Act (Public Law 108–282) amended the Federal Food, Drug, and Cosmetic Act (the FD&C Act) to provide incentives for the development of new animal drugs for use in minor animal species and for minor uses in major animal species. The MUMS Act defines ''minor use'' as ''the intended use of a drug in a major species for an indication that occurs infrequently and in only a small number of animals or in limited geographical areas and in only a small number of animals annually'' (section 201(pp) of the FD&C Act (21 U.S.C. 321(pp))). The major species are cattle, horses, swine, chickens, turkeys, dogs, and cats (section 201(nn) of the FD&C Act (21 U.S.C. 321(nn))).

Prior to enactment of the MUMS Act, FDA defined by regulation minor use to mean ''the use of: * * * (b) new animal drugs in any animal species for the control of a disease that (1) occurs infrequently or (2) occurs in limited geographical areas'' (formerly 21 CFR 514.1(d)(1)). The MUMS Act narrowed this definition by restricting it to uses ''in only a small number of animals annually'' (section 201(pp) of the FD&C Act).

The legislative history of the MUMS Act indicates that Congress intended that FDA further define by regulation minor use in a major species and that it do so ''by evaluating, in the context of the drug development process, whether the incidence of a disease or condition occurs so infrequently that the sponsor of a drug intended for such use has no reasonable expectation of its sales generating sufficient revenues to offset the cost of development'' (see S. Rept. 108–226 at 12–13). The legislative history also notes that the new statutory definition for minor use ''incorporates the existing definition in the Code of Federal Regulations (21 CFR 514.1(d)(1)) with a further limitation to small numbers to assure that such intended uses will not be extended to a wider use'' (see S. Rept. 108–226 at 12–13).

Therefore, while the MUMS Act establishes incentives for animal drug development for minor uses, it also limits the availability of those incentives in order to prevent them from stimulating ''wider use'' of new animal drugs marketed under MUMS Act provisions.

Consistent with these dual aims of stimulating animal drug development for minor uses in major species and at the same time preventing ''wider use'' of such new animal drugs, the agency is now defining the term ''small number of animals'' by establishing for each major species a number that would constitute the upper limit of a ''minor use'' under the MUMS Act. In keeping with the goal of creating a drug development incentive, this definition establishes the number of animals eligible to be treated annually based on the number of animals that represents a drug market value that (relative to drug development costs) would not be likely to be pursued

in the absence of the MUMS Act incentives.

II. Comments

The agency received comments from seven organizations or individuals on the March 2008 proposed rule. Comments were received from a trade organization representing new animal drug manufacturers, a trade organization representing turkey producers, a professional association representing veterinarians, an organization concerned with the ethical treatment of animals, an animal pharmaceutical manufacturer, a law firm representing an unidentified client, and a consumer.

(Comment 1) One comment indicated unqualified support for the March 2008 proposed rule and three additional comments stated appreciation for the agency's attempt to establish what was variously described as a ''quantitative,'' ''reasonable,'' ''bright-line,'' ''understandable,'' or ''easy to use'' approach for determining whether an intended use of an animal drug in a major species is a minor use. However, all of the latter comments went on to note various concerns with the proposed approach which are addressed in the following paragraphs.

(Response) FDA appreciates the characterization of its attempted approach as ''quantitative,'' ''reasonable,'' ''bright-line,'' ''understandable,'' and ''easy to use.''

(Comment 2) Three comments indicated that the agency should not establish ''fixed'' or ''static'' small numbers, but instead should establish the small numbers as a percentage of each major species population. Also, three comments stated that, if the agency did elect to use fixed or static numbers, the small numbers (or the entire approach) should be reevaluated at least every 5 years—preferably, more frequently. The comments stated or implied that the suggested reevaluation was associated with the potential for increasing populations of a major species. An additional comment suggested periodic reevaluation of the small numbers based on the potential for an increase in the cost of drug development.

(Response) FDA agrees that there is a need to periodically reevaluate the definition of ''small number of animals.'' Because Congress did not establish by statute what a ''small number'' is, it affords FDA the opportunity to periodically reevaluate and update the definition of ''small number of animals'' as necessary. We further agree that such a reevaluation should take into account the potential for increases in the development cost of new animal drugs, but note that it also should take into account potential increases in the cost that animal owners are willing to pay to treat affected animals as well as other factors involved in establishing ''small numbers,'' such as changes in the total population of major animal species.

As Congress noted in the legislative history of the MUMS Act, it is the relationship between the development cost of an animal drug and the potential market value of an animal drug that determines the need for the minor use drug development incentives provided by the MUMS Act (see S. Rept. 108–226 at 12–13). If the number of animals affected by a given disease is great enough to produce a market potential sufficient to support the development cost of an animal drug in the absence of the minor use incentives of the MUMS Act, then the incentives should not be provided. The incentives should be reserved for cases in which the number of animals affected by a disease is not great enough to produce a market potential sufficient to support the development costs of an animal drug in the absence of the minor use incentives of the MUMS Act.

With respect to population increase as a basis for reevaluation of ''small numbers,'' if the number of animals affected by a disease increases over time due to increasing rate of occurrence of the disease in the population, or simply due to an increase in the total population of animals with a steady rate of disease occurrence, the market value of a drug intended to treat the disease would also tend to increase and the need for minor use incentives to support drug development for that disease would tend to decrease—unless animal drug development cost or other factors change to a greater extent over the same period of time. Therefore, the effects of population change need to be evaluated in the context of periodically reevaluating other factors affecting the establishment of ''small numbers.''

If the relationship between drug development cost and drug market value changes sufficiently over time, the ''small number of animals'' should change as well. Note, however, that once a particular new animal drug has been designated for a particular intended use that has been determined to be a minor use, the designation and associated incentives will not be affected by subsequent changes in drug market value or published ''small numbers'' (see § 516.29(h) (21 CFR 516.29(h))).

Further reason for periodic reevaluation of the ''small numbers'' is that either the agency may have misperceived the current relationship between development cost, market value, and the value of the MUMS minor use incentives, or the animal pharmaceutical industry's perception of the relationship between these factors sufficient to support drug development could change over time.

In any event, as noted previously, FDA agrees that the ''small numbers'' should be periodically reevaluated and intends to do so. FDA will update the numbers through proposed rulemaking, as warranted, based on the results of the reevaluation.

(Comment 3) Two comments suggested that FDA not implement the proposal at all and that the agency make minor use determinations on a case-by-case basis.

(Response) The agency began making minor use determinations ''on a case-by-case basis'' in the absence of published ''small numbers'' over 3 years ago, but found that it could not equitably do so without establishing a standard against which to assess the individual cases.

The agency had no reasonable basis to establish different small numbers for the same intended use depending upon the relative efficiency of each sponsor's drug development processes. Nor could it determine any practical basis to equitably establish a different small number for every intended use based on perceived potential drug market value for each of those uses.

As explained in the preamble to the March 2008 proposed rule, the agency determined that the most equitable means of establishing the small number for each major companion animal species was to use the best available information regarding the relationships between the number of animals eligible to be treated, the potential value of drug treatment for those animals, and the cost of animal drug development to establish a single small number for each major species that would apply for all new animal drugs. Evaluating the relationship between these factors on a case-by-case basis would require sponsors to divulge, and the agency to assess, information regarding the cost of development of specific animal drugs. Sponsors are reluctant to share such information with the agency.

Small numbers for major food animal species were established on a different basis and this process is discussed in response to comment 11 of this document.

Additionally, making one small number for each major species publicly available permits sponsors to independently assess, early in the drug development process, the likelihood that particular potential intended uses

will qualify as minor uses and plan drug development accordingly.

(Comment 4) Two comments indicated that obtaining epidemiological data on animal disease prevalence is ''difficult to impossible'' or ''almost impossible'' to obtain. One comment was apparently made as a basis for arguing against the establishment of small numbers, and the other for the purpose of requesting information regarding how such information might be obtained.

(Response) The agency indicated in the preamble to the 2005 proposed designation regulation that, in order to document minor use status, sponsors needed to provide an estimate of the number of animals eligible to be treated for a particular intended use per year (70 FR 56394 at 56400, September 27, 2005). We acknowledged at that time that such information ''is not readily available for uncommon animal diseases or conditions.'' Nevertheless, there is clearly no way to determine whether the population of animals eligible to be treated for a given disease or condition meets the statutory standard of a small number of animals without determining the number of animals eligible to be treated in the first place.

Whether the agency determines that the population of animals eligible to be treated is a small number by means of applying the objective standard used in this regulation, or by means of some undefined subjective process applied on a case-by-case basis, it does not alter the need to know, in the first place, the number of animals subject to the intended use under consideration.

Fortunately, based on our experience in reviewing requests for minor use determination up to this point, it has not been as difficult as expected to obtain sufficient information to determine whether an indication qualifies as a minor use. In fact, of the designation requests involving non-aquatic species, most have involved minor use in major species. Of these designation requests, more have been granted for minor use in major species than for minor species. Thus, it has routinely proven possible to gather the needed information regarding animal disease occurrence, and this information has been sufficient to support determinations that an intended use actually is a minor use. FDA, therefore, does not agree with the comments that it is ''almost impossible'' to obtain such information.

With respect to the comment that requested information on how to obtain such information, most of the determinations of minor use made by FDA to this point have been based on a compilation of information available in the veterinary literature. In some cases, this information was augmented with unpublished information available from databases containing information on the rate of occurrence of animal diseases, or the results of surveys of appropriate veterinary experts conducted by sponsors or other (third) parties. In at least one case, the determination was based almost exclusively on a sponsor-initiated survey of veterinary experts conducted in accordance with sound statistical practices.

(Comment 5) One comment suggested that FDA should support conditional approval and exclusivity to the greatest extent possible even when the number of animals involved exceeds a small number.

(Response) While we appreciate the commenter's position with respect to the maximization of the minor use incentives, the MUMS Act limits the incentives associated with the development of drugs intended for minor use in major species to intended uses involving a ''small number of animals.'' This statutory restriction prevents FDA from extending MUMS Act provisions to indications in major species that exceed the ''small number'' restriction.

(Comment 6) One comment stated that FDA should not provide an incentive to develop any animal drug product intended for use in industrial aquaculture or agribusiness.

(Response) The MUMS Act does not contain any language excluding ''agribusiness'' from the incentives of the MUMS Act. The incentives are available to all minor uses in major species, including food-producing animals, with the exception of genetically engineered animals. Industrial aquaculture, referred to by the commenter, deals entirely with minor species and minor species are outside the scope of this regulation.

Just as the agency could not ignore a statutory restriction in response to the previous comment, FDA cannot exclude ''agribusiness'' from the MUMS Act provisions in response to this comment when such a restriction does not appear in the statutory language.

(Comment 7) One comment stated that the preamble to the March 2008 proposed rule implies that the purpose of the limitation of minor use to a small number of animals is to prevent wider use and that this contradicts a statement made in the response to a comment on the 2005 proposed designation regulation, which the commenter summarized as ''the purpose (of defining a subset of a major species which may have a particular disease or condition) is not to prevent a drug with MUMS approval for disease A from being used in disease B or C.''

(Response) When Congress expressed concern regarding the prevention of ''wider use'' of minor use animal drugs it was in the context of defining the ''small number of animals'' for which a minor use new animal drug may be intended if such drug were to qualify for MUMS Act incentives (see S. Rept. 108–226 at 12–13). The intended use of a new animal drug is the particular use for which an animal drug sponsor intends that it be used as determined through various means, including statements in the labels and labeling. The cited response to a comment on the 2005 proposed designation regulation dealt with the provision to permit sponsors to decrease the number of animals eligible to be treated by a given drug by the subset of animals for which treatment would be medically inappropriate. In trying to clarify this provision, the agency stated what the provision did not do. FDA did not intend to require a sponsor to demonstrate that the drug at issue could not be administered for a use other than the intended use for which a minor use determination was being sought. FDA's intent was for the MUMS incentives to be available for drug products for labeled intended uses involving a small number of animals.

In the agency's judgment, because neither the ''wider use'' concept articulated by Congress nor the specific provision of the 2005 proposed designation regulation just discussed were intended to involve any use of an animal drug beyond the scope of its intended use, the agency's statements in the recent preamble to the March 2008 proposed rule and in the cited response to a comment on the 2005 proposed designation regulation are consistent.

(Comment 8) One comment noted that the 2007 final designation regulation (72 FR 41010, July 26, 2007) uses the phrase ''* * * total number of animals to which the drug could potentially be administered on an annual basis'' whereas the preamble to the March 2008 proposed rule on ''small numbers'' uses the phrase ''* * * eligible to be treated on an annual basis.'' The comment requested clarification of the meaning of the phrases and suggested that something along the lines of ''* * * number of cases * * *'' rather than ''* * * number of animals likely to be treated * * *'' would be more appropriate.

(Response) FDA did not intend any difference in meaning between the phrases ''* * * eligible to be treated on

an annual basis'' and ''total number of animals to which the drug could potentially be administered on an annual basis.''

As noted in the preamble to the 2005 proposed designation regulation, there is a special circumstance involving drug use in food-producing major species in which drugs are administered on a herd or flock basis so that the drug is administered to animals that do not have the disease or condition. The 2005 proposed designation regulation takes note of this special circumstance, because the phrase ''* * * number of animals to which the drug could potentially be administered on an annual basis * * *'' is followed by the phrase ''* * * including animals administered the drug as part of herd or flock treatment * * *.''

The 2005 proposed designation regulation needed to capture the special case of herd or flock treatment as well as the general principle involved in establishing the population of animals to which a drug might be administered for a particular intended use. As previously noted, it is this total population of animals that the agency relied upon to establish the market potential on an annual basis for the drug under consideration and this market potential, in turn, was a primary factor in establishing the ''small numbers'' in this final rule.

(Comment 9) A related comment requested clarification of the phrase ''on an annual basis'' and suggested that the phrase should be interpreted to mean that the small number of animals would include only new cases of a disease or condition appearing each year, that is, what is typically referred to as the ''incidence'' of a disease or condition in any given year rather than the total number of cases of the disease or condition existing during the year, that is, what is typically referred to as the ''prevalence'' of the disease or condition over the course of the year.

(Response) The agency devoted considerable discussion to this issue in the preamble to the 2005 proposed designation regulation. We concluded that it is the total number of animals, on an annual basis, eligible to be treated or, in some circumstances (in accordance with the previous discussion), the total number of animals that could potentially be administered a drug for a particular intended use (i.e., including whole herds or flocks that might be treated) that represents the annual market potential for an animal drug and, therefore, it is this population of animals that is of concern to the agency. Also, as noted in the preamble to the 2005 proposed designation regulation, because of the variability in the time course of diseases and the variability in life-span of the seven major species of animals, general application of either of the terms ''prevalence'' or ''incidence'' would not be particularly helpful (70 FR 56394 at 56397).

Experience gained in reviewing the veterinary literature in support of requests for minor use determination has led to the understanding that there is considerable inconsistency in how the terms ''incidence'' and ''prevalence'' are used with respect to the reporting of estimates of animal disease occurrence. Therefore, the agency is less concerned with the formal definitions of ''incidence'' and ''prevalence'' relative to the way the terms are used in the context of describing any particular study or body of information, and more concerned with the manner in which a study is performed or information is captured relative to its ability to contribute to an estimate of the total population of animals eligible to be treated for a given disease or condition over the course of a year. As a result, FDA relied upon the total number of animals ''eligible to be treated on an annual basis'' to define ''small numbers'' rather than relying on ''incidence'' or ''prevalence'' of disease.

(Comment 10) Another related comment requested clarification of whether the ''small numbers'' refer to the number of ''animals'' or the number of ''treatments'' on an annual basis.

(Response) The small numbers refer to the number of animals, not the number of treatments, on an annual basis.

Depending on the nature of the disease or condition involved, the treatment of a given animal could consist of a single short course of treatment or could require repeated administration of a drug over a significant period of time, potentially for the entire life of the animal subsequent to the initiation of treatment. Each year that an animal with such a disease or condition lives after the initiation of treatment, it constitutes part of the population of animals eligible for treatment in that year and, therefore, it is part of the market potential for the drug (or drugs) with which it is being treated for that year.

(Comment 11) One comment stated that the agency should consider turkeys to be a quasi-minor species, and that in setting the small number for turkeys the agency should consider that a much higher percentage of turkeys are treated by feed or water on a flock basis than sheep, which are more commonly treated on an individual animal basis.

(Response) The MUMS Act defines turkeys as a major species (section 201(nn) of the FD&C Act). FDA cannot change that definition without a statutory change.

With respect to factoring the method of drug administration into the comparison between turkeys and sheep that was utilized to establish the small number for turkeys, we note that the agency operated on the assumption that all of the sheep existing in the United States in 2004 were eligible to be treated and further assumed that all of the sheep going to slaughter in that year had been treated. Because the assumption was that 100 percent of sheep going to slaughter were treated that year, regardless of the method of drug administration, the treatment rate could not have been any higher if the sheep were treated on a flock basis rather than an individual basis. As a result, the method of drug administration does not affect the small number FDA established for turkeys.

(Comment 12) One comment stated that many compounds that could be developed for a small number of companion animals are likely to be ''specialty compounds'' and/or new classes of drugs that are likely to have substantially higher development costs than the estimate provided in the March 2008 proposed rule, and that, therefore, the agency should utilize an estimated development cost for minor use new animal drugs of $25 million rather than $15 million.

(Response) While development costs for some minor use new animal drugs could exceed the $15 million estimate utilized by the agency in the process of establishing small numbers, we note that the estimates of development costs for companion animal drugs provided by the animal pharmaceutical industry itself generally fall in the range of $10 million to $20 million with a number of estimates as low as $5 million (Ref. 1). There is no evidence to show that the development of ''specialty compounds and/or new classes of drugs'' is unique to minor uses. Moreover, the industry's estimate of its development costs for companion animal drugs did not capture an estimate as high as $25 million even in its overall range of development costs. This indicates that a development cost for a companion animal drug as high as $25 million would be unusual.

In addition, we note that drugs that could be developed for relatively rare conditions in animals are often also under development, or have already been developed, for similar or related conditions in humans so that the relative infrequency of an intended drug use in animals may not correlate with a higher than usual development cost.

Therefore, the agency determines that there is currently no convincing information available to support increasing its estimate of companion animal drug development cost, but will periodically reexamine this estimate along with others supporting the establishment of small numbers for major companion animal species to determine whether the small numbers need to be revised.

(Comment 13) One comment stated that the agency's estimate of $10 million for third-year sales of a companion animal drug was too high for a minor use drug, and that the figure should be lowered to $3 million.

(Response) The agency determined the $10 million figure on the basis of animal drug marketing principles provided by outside experts in the development of animal drugs (Ref. 1). As noted in the preamble to the March 2008 proposed rule, one of those basic principles was that, taking into consideration the current animal drug development incentives associated with exclusivity under the Generic Animal Drug and Patent Term Restoration Act, a sponsor would need to perceive a potential third-year market value for an animal drug equivalent to the development cost of the drug in order to pursue development (73 FR 14411 at 14413). The agency received no comments that contradicted the validity of this basic principle.

The agency also relied on the principle that the 7 years of exclusive marketing rights provided to MUMS drugs ''provides a sponsor an opportunity to lower its perception of an acceptable 'going' market value to support drug development because the sponsor has longer to recoup development costs without competition'' (73 FR 14411 at 14413). Again, the agency received no comments opposing the validity of this basic principle.

The agency then applied these two principles to estimate that the quantitative effect of the additional 2 years of exclusivity associated with the approval of a designated minor use drug was to lower the perceived third-year drug market value needed to support a decision to develop a drug by about one-third (73 FR 14411 at 14413). The agency received no comments opposing the validity of the general conclusion drawn from the application of the basic principles noted in the previous paragraphs.

The figure of $10 million as the perceived third-year market necessary to support the development of a drug with a $15 million development cost is simply the result of applying the general conclusion to a reasonable estimate of the development cost of a companion animal drug.

The implication in the comment that many companion animal drugs have been developed in the past for intended uses whose third-year market values were less than the agency's $10 million estimate could be interpreted in a number of ways, including the following: That the development cost for the drugs was less than $10 million; that the sponsors involved were willing to accept a return on investment lower than a third-year market equal to development costs when they made the decision to develop the drugs; and/or that actual market values routinely fail to achieve the potential market value perceived by sponsors, on the basis of which sponsors decide to develop drugs.

Of these possible interpretations, the latter appears the most improbable, because it is unlikely that animal drug sponsors could survive the economic consequences of routinely failing to accurately predict potential markets. The other two possibilities appear to support a conclusion that the agency may have overestimated drug development cost and/or the perceived return on investment needed to support animal drug development.

Therefore, the implication that third-year market values less than $10 million have routinely supported animal drug development in the past (in the absence of the MUMS incentives), argues in favor of decreasing estimated drug development cost or decreasing the estimated 1:1 relationship between development cost and perceived third-year market value (absent the value of MUMS exclusivity) that the agency assumed was needed to support animal drug development. This would lead to a decrease in the estimated size of the population of animals eligible to be treated that is needed in order to provide a market value sufficient to support drug development.

The agency notes in passing that the comment stating that the agency's estimate of third-year market value needed to support companion animal drug development was too high tends to contradict the preceding comment (comment 12 of this document) which argued that the agency's proposed estimate of companion animal drug development cost for a minor use was too low. More significantly, no comments provided evidence to support decreasing either the proposed estimate of companion animal drug development cost or of the 1:1 relationship between development cost and perceived market value (absent the value of MUMS exclusivity) that the agency assumed was needed to support animal drug development. However, the agency will periodically reexamine these estimates along with others supporting the establishment of small numbers for major companion animal species based on newly available information regarding drug development costs and other factors to determine whether the small numbers need to be revised.

(Comment 14) One comment stated that production costs would be relatively higher for drugs intended for the small number of animals associated with minor use because such drugs lack the economy of scale associated with the production of drugs intended for larger numbers of animals.

(Response) While it is possible that production costs could be a determining factor in the decision to develop a particular drug product for a particular minor use, it appears that many other factors are considerably more important in determining the price of a drug product and, therefore, its market value, and that differences in cost associated with scale of production would rarely be the determining factor in the decision to develop a drug for a minor use (Ref. 2).

Thus far, sponsors seeking minor use determinations have not expressed concern to FDA regarding the effect of limited market size on the cost of drug production.

Therefore, the agency is not convinced that, in general, the potential impact of this factor is sufficient in itself to prevent the development of animal drugs for minor uses in accordance with the small numbers of animals established by this regulation.

(Comment 15) One comment stated that, for a variety of reasons, the agency should consider the drug treatment rate for minor uses in companion animals to be 25 percent rather than 50 percent.

(Response) A number of independent sources appear to agree that a reasonable estimation of the treatment rate for companion animals is on the order of 50 percent (Ref. 3). The comment does not appear to take exception to this as a general estimate of companion animal treatment rate, but argues that it is too high for ''a rare condition * * * especially in the first years of a new drug's availability'' because ''many of these conditions have a poor prognosis or occur in older pets for which the owner is more likely to do nothing or consider euthanasia'' and that the utilization of a drug for a minor use is ''likely to be slower due to higher cost, limited distribution, and less promotion'' than for a major use.

The agency believes that a companion animal owner's decision to treat has a great deal to do with the seriousness of the disease or condition involved, the cost of treatment, and the emotional value of a pet, and has relatively little to do with the rarity of the disease or condition warranting treatment. There is no reliable information to conclude that the treatment rate of a rare disease would be routinely lower than the treatment rate of a common disease, simply on the basis that it is rare.

Based on FDA's experience with minor use determinations thus far, the agency believes that a primary characteristic of the drugs pursued for minor uses in animals under the incentives provided by the MUMS Act will be for uses where there is a long-established need for treatment and no legally available, practical, or affordable treatment option. Because these intended uses most often involve diseases or conditions that are relatively serious and that result in considerable animal suffering, in the absence of legal, practical, safe and effective treatment options an animal owner might turn to euthanasia. However, if an effective treatment were available these are the kinds of diseases and conditions that animal owners would be inclined to treat once a definitive diagnosis was made, irrespective of the frequency of occurrence of the disease or condition in the population (see the results of the surveys cited in the following paragraphs).

Under these circumstances, the factors most likely to affect an animal owner's decision to treat are the pet's perceived value, the cost of treatment, and the potential effects, positive and negative, of treatment. In any particular case in which a veterinarian concludes that the risks associated with treatment outweigh the benefits, the appropriate course of action would be a recommendation of no treatment or euthanasia (depending on the prognosis for an untreated animal). This would be true regardless of the cost of the treatment or whether the disease or condition is rare or common. When a veterinarian concludes that the benefits of treatment outweigh the risks, depending upon the nature of the treatment recommended, the animal owner is faced with a decision that could very well depend upon the cost of treatment relative to the prognosis.

Therefore, the agency gathered considerable information relating to the willingness of companion animal owners to treat serious (significantly debilitating or life-threatening, if untreated) diseases or conditions in their pets in the process of estimating both practical drug treatment values and the likelihood of treatment. The agency found the following:

A 1999 report commissioned by the American Veterinary Medical Association, the American Animal Hospital Association, and the Association of American Veterinary Medical Colleges (Ref. 4) states that:

- Pet owners say they would pay $688 for a 75 percent chance of successfully treating their pet and $356 for only a 10 percent chance of a successful treatment.
- Pet owners say they would pay an average of $1,042 to keep their favorite pet (dog) from dying and $657 to keep their favorite pet (cat) from dying.
- Horse owners would pay an average of $1,827 for a 75 percent chance of successfully treating their horse and $828 for a 10 percent chance.
- Horse owners say they would pay an average of $3,314 to keep their favorite horse from dying and $2,010 for their least favorite horse.

A 2002 survey of pet owners by the American Animal Hospital Association found that 73 percent of pet owners would go into debt to provide for their pet's well-being and 73 percent would spend from $1,000 up to any amount in a life-threatening situation (Ref. 1).

A 2003 survey of veterinarians by DVM Magazine found that, among companion animal practitioners, the cost at which a majority of pet owners would refuse treatment was just under $1,100, and that 26 percent of pet owners would treat regardless of price and an additional 34 percent would treat in accordance with all of the veterinarian's recommendations (Ref. 5).

A 2005 survey of pet owners by Hartz Mountain found that 32 percent said that money was no object when it came to their pet's health (Ref. 6).

These surveys demonstrate that companion animal owner willingness to care for their animals regardless of cost has increased over time, and may have continued to increase since the surveys noted in the previous paragraphs. Given this information, it is difficult to conclude that cost alone would decrease treatment rates for serious diseases or conditions below the estimate of 50 percent proposed by the agency.

With respect to the comment that treatment rate would be negatively influenced by the lack of awareness of, or simply the lack of availability of, a drug once it was developed, approved, and marketed, due to limited promotion or distribution, we note again that many minor uses involve conditions or diseases for which no practical and legal treatment options exist and for which effective treatments may have been desired by veterinarians for years. Under such circumstances, it should not take a significant effort to either inform veterinarians of the availability of a drug for such a disease or condition or to convince them of the need for it.

Therefore, the agency determines that there is currently no reliable evidence to support decreasing the proposed estimate of drug treatment rate for minor uses in companion animals, but will periodically reexamine this estimate along with others supporting the establishment of small numbers for major companion animal species to determine whether the small numbers need to be revised.

(Comment 16) One comment stated that a manufacturer receives approximately 25 percent of the actual cost paid by an animal owner for drug treatment, that the rest goes to those involved in drug distribution up to the point of treatment, and, therefore, that a more appropriate drug treatment value for dogs would be $100 rather than $350.

(Response) The $350 referenced by the comment represents the agency's estimate of the drug treatment value to the manufacturer for a product intended for use in dogs in order to justify drug development for an uncommon, but serious condition—with the understanding that the price to the animal owner would be significantly higher.

While there may be circumstances under which a manufacturer would receive only 25 percent of the actual cost paid by an animal owner for drug treatment, the agency does not agree that 25 percent represents the typical manufacturer share of the cost to an animal owner for new animal drugs of the kind that are likely to qualify for minor use status.

The manufacturer's price for a new animal drug product and the subsequent prices of those involved in the distribution of the product to the animal owner are significantly affected by a number of factors including the nature of the drug involved, the significance of the intended use of the product, the availability of alternative products for the intended use, and ultimately by the amount that animal owners are willing to pay to treat their animals for particular intended uses (see the results of the surveys cited in the response to the previous comment).

Based on the information available to the agency, a more typical example of pricing for a product with an intended use in dogs that would qualify for minor use status would be about $350 from a manufacturer to a distributor, $440 from a distributor to a veterinarian, and $880

from a veterinarian to an animal owner. Thus the manufacturer would receive approximately 40 percent of the cost of the drug to the animal owner. However, for expensive drugs veterinarians may be willing to decrease their price from the routine 200 percent of their cost to something on the order of 135 to 150 percent which would result in a price to the animal owner of about $590 to $660. In this case, the manufacturer would receive approximately 50 to 60 percent of the cost of the drug to the animal owner (Ref. 2).

As explained in response to comment 15 of this document, even a final drug price of $880 would likely be acceptable to most dog owners for the treatment of a serious condition.

The information available to the agency, as cited previously, does not support the comment's assertion that manufacturers receive only 25 percent of the final cost to the animal owner of a new animal drug. However, FDA will periodically reexamine this estimate to determine whether the small numbers need to be revised.

III. Legal Authority

FDA's authority for issuing this final rule is provided by the MUMS Act (section 571 of the FD&C Act *et seq.* (21 U.S.C. 360ccc *et seq.*)). When Congress passed the MUMS Act, it directed FDA to publish implementing regulations (see 21 U.S.C. 360ccc note). In the context of the MUMS Act, the statutory requirements of section 573 of the FD&C Act (21 U.S.C. 360ccc-2), along with section 701(a) of the FD&C Act (21 U.S.C. 371(a)) provide authority for this final rule. Section 701(a) authorizes the agency to issue regulations for the efficient enforcement of the FD&C Act.

IV. Analysis of Economic Impacts

FDA has examined the impacts of the final rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order 12866 directs 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 final rule is not a significant regulatory action under the Executive order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because the final rule is only expected to slightly reduce the administrative effort of ''minor use'' requestors while imposing no additional costs, the agency certifies that the final rule would not have a significant economic impact on a substantial number of small entities.

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 $133 million, using the most current (2008) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this final rule to result in any 1-year expenditure that would meet or exceed this amount.

FDA previously published both a proposed rule and final rule on the MUMS designation system. Each of these publications included analyses of the expected economic impacts of the creation and administration of the MUMS designation system as required by the Executive order and two statutes mentioned in the previous paragraphs. The 2007 final designation regulation presented estimates of the annual costs of the MUMS designation system of about $65,000 annually. Additionally, the 2007 final designation regulation provided some discussion of, but was not able to quantify, the expected benefits of the regulation.

The 2007 final designation regulation included a statement that FDA would address the issue of establishing a definition of ''small number of animals'' in a future rulemaking. In the March 2008 proposed rule, FDA proposed a specific ''small number of animals'' for each of the seven major animal species as defined by the MUMS Act, based on the data and analysis described in its preamble.

The March 2008 proposed rule, which this rule finalizes, sets an upper limit on the number of animals of each of the seven major animal species for which a request for designation could be made under the ''minor use'' provisions of the 2007 final designation regulation. When proposing the rule, FDA did not have any additional information to show that the proposed threshold numbers would significantly affect the expected number of MUMS designation requests that are received by the agency each year. The definition of a ''small number'' of each of the seven major species reduces the ambiguity for ''minor use'' requestors. Additionally, the rule provides for a small reduction in administrative effort by ''minor use'' requestors who are no longer required to provide additional information on potential markets and drug development costs due to the proposed removal of § 516.21(c) (21 CFR 516.21(c)).

FDA did not receive any comments pertaining to the analysis of impacts section of the March 2008 proposed rule. Further, FDA has not made any substantive changes to this final rule that would require significant changes to the assumptions used, and conclusions reached, in the impacts section of the March 2008 proposed rule. As such, FDA retains its impacts analysis of the March 2008 proposed rule for this final rule. FDA has determined that the final rule would not impose any additional costs or provide any further health benefits beyond those contained in the 2007 final designation regulation.

V. Paperwork Reduction Act of 1995

This final rule does not contain new information collection provisions that would be subject to review by the Office of Management and Budget (OMB), under the Paperwork Reduction Act of 1995 (the PRA) (44 U.S.C. 3501–3520).

Title: Setting ''Small Numbers of Animals'' for Determining Minor Use

Description: This final rule revises the minor use provisions of 21 CFR part 516, subpart B. Part 516 contains the implementing regulations for the MUMS Act and subpart B contains the designation provisions for minor use and minor species new animal drugs. Currently, requests for minor use designation are considered on a case-by-case basis by the agency under a regulation (§ 516.21) requiring that product-specific financial information supporting minor use status be included in the request. In order to further define minor use, this rule provides seven threshold ''small numbers of animals,'' one for each major species, based on industry-wide economic or animal production data. With these numbers in place, drug sponsors requesting minor use designation will no longer be required to submit the confidential product-specific financial information described in § 516.21(c). Therefore, the reporting burden for minor use designation, as currently required in § 516.20(b)(7), will be somewhat lower. However, we anticipate that many requests for designation will be for minor species, not minor use, and furthermore, the current requirement for financial information is only one part of

a request for designation, therefore, the total paperwork burden currently assigned to § 516.20 will not be affected significantly.

This final rule also refers to previously approved collections of information found in FDA regulations. These collections of information are subject to review by OMB under the PRA. The collections of information in § 516.20 have been approved under OMB control number 0910–0605.

VI. Environmental Impact

We have carefully considered the potential environmental impacts of this final rule and determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment, nor an environmental impact statement is required.

VII. Federalism

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the agency has concluded that the rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

VIII. References

The following references have been placed on display in the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Brakke Consulting, Inc., ''Disease Incidence Rates, Drug Development and Treatment Costs,'' September 2005.

2. Brakke Consulting, Inc., ''Pharmaceutical Pricing for Companion Animal Products,'' December 2008.

3. American Veterinary Medical Association, ''U.S. Pet Ownership & Demographics Sourcebook,'' 2002.

4. Brown, J.P., and J.D. Silverman, ''The Current and Future Market for Veterinarians and Veterinary Medical Services in the United States,'' *Journal of the American Veterinary Medical Association*, vol. 215, No. 2, July 15, 1999.

5. Verdon, D.R., ''Clients Spending More Before Stopping Treatment, DVMs Say,'' DVM Newsmagazine, July 1, 2003.

6. PR Newswire, ''New National Hartz Survey on the Human-Animal Bond Finds That Pets Are Seen as Part of the Family by Three in Four Pet Owners,'' April 2005.

List of Subjects in 21 CFR part 516

Administrative practice and procedure, Animal drugs, Confidential business information, Reporting and recordkeeping requirements.

■ Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 516 is amended as follows:

PART 516—NEW ANIMAL DRUGS FOR MINOR USE AND MINOR SPECIES

■ 1. The authority citation for 21 CFR part 516 continues to read as follows:

Authority: 21 U.S.C. 360ccc-1, 360ccc-2, 371.

■ 2. Amend § 516.3 by alphabetically adding a new definition to paragraph (b) as follows:

§ 516.3 Definitions.

* * * * *

(b) * * *

Small number of animals means equal to or less than 50,000 horses; 70,000 dogs; 120,000 cats; 310,000 cattle; 1,450,000 pigs; 14,000,000 turkeys; and 72,000,000 chickens.

* * * * *

§ 516.21 [Amended]

■ 3. Amend § 516.21 by removing paragraph (c).

Dated: August 18, 2009.

David Horowitz,

Assistant Commissioner for Policy.

[FR Doc. E9–20553 Filed 8–25–09; 8:45 am]

BILLING CODE 4160–01–S

DEPARTMENT OF HOMELAND SECURITY

Coast Guard

33 CFR Parts 100, 147, and 165

[USCG–2009–0777]

Quarterly Listings; Safety Zones, Security Zones and Special Local Regulations

AGENCY: Coast Guard, DHS.

ACTION: Notice of temporary rules issued.

SUMMARY: This document provides required notice of substantive rules issued by the Coast Guard and temporarily effective between January 2007 and January 2008, that expired before they could be published in the **Federal Register**. This document lists temporary safety zones, security zones, and local regulations, all of limited duration and for which timely publication in the **Federal Register** was not possible.

DATES: This document lists temporary Coast Guard rules between 8 January 2007 and 30 January that became effective and were terminated before they could be published in the **Federal Register**.

ADDRESSES: The Docket Management Facility maintains the public docket for this notice. Documents indicated in this notice will be available for inspection or copying at the Docket Management Facility (M–30), U.S. Department of Transportation, West Building, Ground Rloor, Room W12–140, 1200 New Jersey Avenue, SE., Washington, DC 20590 between 9 a.m. and 5 p.m., Monday through Friday, except Federal holidays.

FOR FURTHER INFORMATION CONTACT: For questions on this notice contact Yeoman First Class Denise Johnson, Office of Regulations and Administrative Law, telephone (202) 372–3862. For questions on viewing, or on submitting material to the docket, contact Ms. Angie Ames, Docket Operations, telephone 202–366–5115.

SUPPLEMENTARY INFORMATION: Coast Guard District Commanders and Captains of the Port (COTP) must be immediately responsive to the safety and security needs within their jurisdiction; therefore, District Commanders and COTPs have been delegated the authority to issue certain local regulations. Safety zones may be established for safety or environmental purposes. A safety zone may be stationary and described by fixed limits or it may be described as a zone around a vessel in motion. Security zones limit access to prevent injury or damage to vessels, ports, or waterfront facilities and may also describe a zone around a vessel in motion. Special local regulations are issued to enhance the safety of participants and spectators at regattas and other marine events. Timely publication of these rules in the **Federal Register** is often precluded when a rule responds to an emergency, or when an event occurs without sufficient advance notice. The affected public is, however, informed of these rules through Local Notices to Mariners, press releases, and other means. Moreover, actual notification is provided by Coast Guard patrol vessels enforcing the restrictions imposed by the rule. Because **Federal Register** publication was not possible before the beginning of the effective period,