Note: MT controls apply to "software" specially designed or modified for the "development", "production", or "use" of equipment controlled for MT by 4A01, 4A02, 4A03, and 4A21.

4D02A "Software" specially designed or modified to support "technology" controlled by 4E for NS or MT.

Requirements

Validated License Required: QSTVWYZ
Unit: $ value
Reason for Control: NS, MT, FP (see Note)
GTDR: Yes, *except* MT, Iran and Syria
GTDU: No

Note: MT controls apply to "software" specially designed or modified to support technology for the "development", "production", or "use" of equipment controlled for MT by 4A01, 4A02, 4A03, and 4A21.

* * * * *

16. Supplement No. 2 to § 799.1 is amended by revising the introductory text of the second note to read as follows:

Supplement No. 2 to § 799.1—General Technology and Software Notes

* * * * *

2. *General Software Note.* General License GTDR, without written assurance, is available to all destinations, except Country Groups S and Z, Iran, and Syria, for release of software that is generally available to the public by being:

* * * * *

Dated: September 4, 1992.

James M. LeMunyon,
Acting Assistant Secretary for Export Administration.

[FR Doc. 92-22037 Filed 9-11-92; 8:45 am]
BILLING CODE 3510-DT-M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 310

[Docket No. 76N-052E]

RIN 0905-AA06

Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use; Expectorant Drug Products for Over-the-Counter Human Use

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule establishing that any over-the-counter (OTC) drug product containing ipecac and certain other active ingredients for use as an expectorant is not generally recognized as safe and effective or is misbranded. (An expectorant is a drug taken orally to promote or facilitate the removal of secretions from the respiratory airways.) This final rule evaluates data on ipecac that were pending review when an earlier final rule on OTC expectorant drug products was issued. Also, this final rule lists in a regulation all OTC expectorant ingredients that have been found to be not generally recognized as safe and effective or are misbranded. This final rule is part of the ongoing review of OTC drug products conducted by FDA.

EFFECTIVE DATE: September 14, 1993.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drug Evaluation and Research (HFD-810), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-295-8000.

SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of September 9, 1976 (41 FR 38312), FDA published an advance notice of proposed rulemaking to establish a monograph for OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products together with the recommendations of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products, which was the advisory review panel responsible for evaluating the data on the active ingredients in these drug classes. One segment of that report dealt with expectorants. The agency's tentative final monograph on OTC expectorant drug products was published in the **Federal Register** of July 9, 1982 (47 FR 30002). Ipecac was classified as Category III (available data are insufficient to classify as safe and effective, and further testing is required). Subsequently, while the administrative record was open, the agency approved a proposed protocol for studying ipecac (Refs. 1, 2, and 3). On January 6, 1987, after the administrative record had closed, a citizen petition was filed with the agency submitting two studies on the effectiveness of ipecac as an expectorant (Ref. 4). The data remained under review at the time of publication of the agency's final rule on OTC expectorant drug products in the **Federal Register** of February 28, 1989 (54 FR 8494 at 8504). The agency's evaluation of those data completes the rulemaking on OTC expectorant drug products.

In the proposed regulation for OTC expectorant drug products (47 FR 30002 at 30003), the agency advised that the conditions under which the drug products subject to this monograph would be generally recognized as safe and effective and not misbranded (monograph conditions) would be effective 12 months after the date of publication in the **Federal Register**. On February 28, 1990, the final monograph became effective. As of that date, no OTC drug product that is subject to the monograph and that contains a nonmonograph condition, i.e., a condition that would cause the drug to be not generally recognized as safe and effective or to be misbranded, could be initially introduced or initially delivered for introduction into interstate commerce unless it was the subject of an approved application. Any OTC expectorant drug product that is subject to the monograph, whether formulated as a single ingredient or a combination drug product, had to meet the requirements of this final rule as of February 28, 1990. Further, any OTC drug product subject to this monograph that was repackaged or relabeled after the effective date of the monograph had to be in compliance with the monograph regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce.

In its final conclusions on OTC expectorant drug products (54 FR 8494 at 8508), the agency listed a number of expectorant ingredients that it considered to be nonmonograph ingredients. At that time, none of these ingredients was listed in a regulation. Since then, the agency has established 21 CFR 310.545 in which it listed certain active ingredients that are not generally recognized as safe and effective for certain OTC drug uses. The agency is adding § 310.545(a)(6)(iii), covering the nonmonograph expectorant active ingredients discussed in the final rule of February 28, 1989. The agency is also including ipecac in this listing. The date of nonmonograph status for all of the ingredients in the list in § 310.545(a)(6)(iii), except ipecac, was February 28, 1990. The date of nonmonograph status of ipecac is September 14, 1993.

References

(1) Comments No. RPT003 and SUP001, Docket No. 76N-052C, Dockets Management Branch (HFA-305), Food and Drug Administration, rm 1-23, 12420 Parklawn Dr., Rockville, MD 20857.

(2) Letters from W. E. Gilbertson, FDA, to H. Jenkins, Creomulsion Co., coded LET080

and LET082, Docket No. 76N–052C, Dockets Management Branch.

(3) Letter from H. Jenkins, Creomulsion Co., to W. E. Gilbertson, FDA, coded LET081, Docket No. 76N–052C, Dockets Management Branch.

(4) Comment No. CP, Docket No. 76N–052C, Dockets Management Branch.

II. The Agency's Final Conclusions on Ipecac for Expectorant Use

As noted above, two studies (Refs. 1 and 2) were submitted purporting to establish the effectiveness of ipecac as an expectorant. Study 1 was a double-blind, placebo-controlled, 2-week trial of parallel design. Its objectives were to evaluate the effectiveness of ipecac syrup (1) in modifying the viscosity and volume of the tracheobronchial secretions and (2) in providing relief of difficult expectoration and cough.

This study involved 40 subjects, 20 in each of 2 groups of hospitalized patients of either sex with chronic bronchitis not associated with asthma, but including annoying tracheobronchial secretions, coughing, and difficult expectoration. The treatment regimens were: (1) 15 milliliters (mL) of a flavored vehicle base as the placebo and (2) 0.041 mL of fluid extract of ipecac U.S.P. XVI in the same vehicle (which is equivalent to 0.82 milligram of total alkaloids). Each treatment was given 3 times a day. Subjects with allergies or known hypersensitivity to ipecac were excluded as well as any subject requiring continuous mucolytic, anticholinergic, antiasthmatic, or steroid therapy, or any other prescription drug which may have affected the study results. The following effectiveness parameters were measured: (1) Result of therapy, (2) sputum volume, (3) sputum characteristics (combination of viscosity and sputum appearance), (4) difficulty expectorating, and (5) severity of cough.

A 3-day wash-out period, during which all mucolytics and liquefacients were to be discontinued and baseline sputum measurements (both the volume and physical characteristics) were to be recorded, was followed by randomization to one of the treatment arms. At 8 a.m. on day 4, the sputum volume designated day 4 was collected, and the drug was first administered. The drug was given 3 times a day at 8 a.m., 12 m., and 4 p.m. thereafter for 14 days.

The sputum volume was collected from 8 a.m. to 6 a.m. the next morning, and it represented the total daily volume. In the petitioner's data analysis, the petitioner states that to determine the day on medication, 4 should be subtracted from the study day number because of the sputum volume collection that occurred on day 4. Thus, the sputum for day 10 of the study would be for the sixth day on medication.

Sputum was collected separately from 6 a.m. to 8 a.m. the same day and was the specimen utilized for the rheologic measurements, using the following numerical scores for the behavior of the specimen when applied to an inclined glass slide: 4 = pus-like with no movement, 3 = stringy and clumps with slow movement, 2 = stringy with slow flow, and 1 = clear with free flow.

The difficulty of expectoration and the severity of cough were subjectively assessed at 8 a.m. each day and employed the following 4-point scale: 0 = no difficulty, 1 = slight effort, 2 = moderate effort, and 3 = requiring great effort.

The recorded objective values for sputum volume indicated that there was an increase in volume for the subjects on active drug during the first week which achieved statistical significance on day 7 (day 3 of treatment) of the trial. The petitioner claims that the volume increased on the first few days, reaching a plateau around the third and fourth days and declining thereafter. The total volume expectorated was the same for both groups over the entire treatment period. The petitioner claims that the ipecac treatment produced a greater fraction of the total volume earlier in the study than did the placebo.

Although sputum volume differences between ipecac and placebo were seen, no statistically significant differences for sputum characteristics (i.e., viscosity) or difficulty of expectoration were noted. The petitioner used a subjective evaluation called "result of therapy" at the end of the study and concluded that the ipecac response was better than the placebo response. However, the agency considers this method of evaluation to be unacceptable in this study because no details about the method were stated except that it was performed once.

The investigators calculated the volume data by "normalizing," i.e., the volumes are expressed as percentages of the baseline mean volume for each subject for each day. When analyzed by three different statistical methods, the petitioner claimed these data show that the values for days 7, 8, and 9 (3, 4, and 5 of treatment) are significantly greater for ipecac than for the placebo.

Of the other three variables measured, i.e., sputum characteristics (measured objectively), ease of expectoration, and severity of the cough, no differences were noted either overall or on any given day.

The investigators concluded that the results indicate that the sputum volume from the subjects on ipecac is increased on days 3, 4, and 5 and that it reached statistical significance on day 3. They state that the response to treatment was better for the ipecac subjects than the placebo subjects. However, his statement was not documented other than by the clinician's subjective evaluation at the end of the study. The objective measurement of sputum volume (expressed as cumulative percent) correlated significantly with the subjective measurement response to treatment.

The agency has determined that a number of important details (as discussed below) were not provided in the data submitted. As a result of these deficiencies, this study as submitted cannot be considered as adequate and well controlled. Additionally, the case report forms that were submitted were handwritten and in Italian. Translation was provided for the more common terms but not for other terms.

No daily record of the use of concomitant medication was provided on the case report forms. On the initial case report form (containing a space for this entry), it appears that approximately one-third of the subjects were given antibiotics at some time during the study. These drugs were administered when superimposed infection complicated the picture of chronic bronchitis. However, their use would influence the volume and qualitative characteristics of the sputum along with other evaluation assessments.

Other concomitant medications (antiasthmatic and diuretic) appear to have been given also. However, the amounts and frequency of such usage were either not recorded on a daily basis, or if that were done, the information was not provided.

The investigators claim that the study results indicate that only one of four efficacy assessments was found to have a difference between the two treatments. This difference was reflected in the volume of sputum and only on day 7 (day 3 of treatment) did the difference reach statistical significance. The total sputum volume for the whole period did not differ between the two groups. Moreover, the increase in volume reported did not correlate with any other improvement, i.e., no reduction in viscosity, no easier expectoration, and no alteration in severity of cough. The investigators used raw data, i.e., the volume for each subject for each day expressed as a mean to support the difference on day 7. Using the same data, no other day showed any difference in volume. The normalized and cumulative volumes of

sputum were also used to compare the results; normalized meaning that the volume for each subject for each day has been calculated as a percentage of the mean sputum volume for that subject during the baseline period. Cumulative values were obtained by summing the sputum volumes for each subject for all medication days (days 5 through 18), dividing this into the sputum volume for that subject for each day, multiplying by 100, and cumulating the volumes beginning on day 5.

Upon examination of the 24-hour sputum volume for both groups, it can be seen that there are subgroups within each group. Subjects 2, 4, 5, 6, and 35 have a smaller daily volume both at baseline and elsewhere than do the others in that group; the same is true for subjects 1, 8, 16, and 32 in the placebo group.

The actual increase in sputum volume produced by ipecac is obscured because subjects who were given the ipecac produced less sputum during the baseline period and also during the period beyond 1 week of ipecac administration than subjects given the placebo. Therefore, sputum volume results for ipecac and placebo samples were "normalized."

The purpose of the baseline period is to establish measurements (values) uninfluenced by extraneous factors and to establish comparability of the treatment groups. Normalizing is acceptable if the intervention introduced into the trial must differ for some reason, i.e., one group receives a larger dose of a drug than the other.

"Normalization" of sputum volume in this study is inappropriate for the following reasons: (1) The results have been normalized only when it could benefit ipecac, (2) "normalization" is not a standard statistical technique. The study reports do not describe how normalization was accomplished; thus, its validity cannot be evaluated, and (3) most important of all, normalization was not considered or planned for in the protocol. Because normalization was not planned before the study results were available, and because normalization was used selectively when it would give a predictably more favorable result for ipecac, the agency considers use of normalization in this study to be invalid. Further, the agency also notes that in Study 2, where normalization would tend to discredit the ipecac results, the sputum volume was not normalized.

Although sputum volume differences between ipecac and placebo were seen, no statistically significant differences for sputum characteristics (i.e., viscosity) or difficulty of expectoration were noted. A subjective evaluation called "result of therapy," made a single time at the end of the study, is used as a basis for concluding that the ipecac response was better than the placebo response. The agency considers this method of evaluation unacceptable in this study.

No details were provided about this "result of therapy" method of evaluation other than the fact that it was performed once at the end of therapy. When a global evaluation is made at the end of a therapeutic period, the physician considers a number of factors that measure treatment effect. The global evaluation is usually made in conjunction with periodic evaluations (overall assessments) also conducted by the physician during the course of treatment. Such terminology is usually applied to multiple variables and is employed in long-term trials, as it is helpful in establishing a timeframe at which certain parameters respond in comparison with overall general improvement. For example, in chronic arthritis, reduction in joint size and pain may be achieved weeks before noticeable improvement in range of motion of a given joint may occur.

The agency concludes that these two studies do not provide sufficient statistical evidence to support the effectiveness of ipecac. Using its own standard of evaluation, the petitioner was unable to show statistically lower viscosity of sputum for subjects receiving ipecac compared to those receiving the placebo. For volume of sputum, only 1 of 14 days (day 7) provided a 1-tail p-value showing greater sputum production using ipecac. Ignoring the fact that 1-tail p-values are not appropriate and that the appropriate 2-tail p-value exceeded 0.05, only 1 of 14 statistical tests led to a statistically significant result.

Further, for the variables "difficulty expectorating" and "severity of cough," the investigators reported that no statistically significant differences were found (pp. 17 and 19 of study report) between ipecac and placebo. For the variable called "patient result of therapy," a statistically significant result was claimed. The agency has reanalyzed the raw data from the subject record forms and is unable to confirm the investigators' claimed statistical result favoring ipecac over placebo.

The agency finds no statistical evidence for Study 1 showing that ipecac is superior to placebo in terms of the secondary efficacy variables of "difficulty expectorating," "severity of cough," and "patient result of therapy."

The agency points out that in a similar study using guaifenesin as the expectorant drug (performed by the same investigators at the same hospital), the results showed an increase in sputum volume that correlated with a decrease in viscosity and in cough (not objectively measured) along with improvement in the ability to bring up sputum easier. The results with ipecac in this study do not show this correlation.

In conclusion, the agency considers Study 1 to be flawed and not an adequate and well-controlled study. Further, the results do not establish the effectiveness of ipecac as an expectorant.

Study 2 was similar to Study 1 with the following differences: (1) There were only 10 subjects in each treatment group. (2) Objective evaluation of the sputum was not done daily, but only on days 1, 3, 6, 9, and 15 (2 days baseline pretreatment and 3 days on therapy). The methodology in this study differed in that a thromboelastograph was employed to evaluate sputum characteristics. This is an instrument which reportedly measures the viscosity/elasticity/cohesiveness of the sputum sample. (3) The effectiveness parameters are not the same as those in Study 1. In this study, the parameters were "sputum volume," "physician's evaluation," "subject's evaluation," and "viscosity/adhesiveness/elasticity" using an "oscillating cup rheometer."

The results of this study were reported to show that sputum volume reached a level 40 percent above the baseline values for the ipecac subjects on days 7, 8, and 9 (days 3 to 5 of treatment). The mean viscosity was said to be less for the ipecac group on days 6, 9, and 15 when compared to baseline values. It is also reported as less than the mean viscosity of the placebo group on the same days. The mean cumulative percent of the total sputum volume is significantly greater for the ipecac group than for the placebo group beginning on day 7 and continuing through day 12. Increases in the sputum volume and decreases in the viscosity were said to correlate significantly with the subjects' and the physician's assessment of the clinical improvement.

The agency notes that the case report forms from this study are also in Italian but, in contrast to those in Study 1, the entries were typed, not handwritten. They contain more information than the case report forms from Study 1.

The agency finds the following problems with this study: (1) Although the subjects were also chronic bronchitics, they were chosen only if they were thought not to require antibiotics. (2) The case report forms do

not mention infection, but 5 subjects (25 percent) received 1 or more antibiotics (3 subjects in the placebo group—number 6, 9, and 19, and 2 subjects in the ipecac group—numbers 8 and 13) which may have influenced sputum changes, volume, and/or viscosity. (3) The number of subjects treated (only 10) is too small. Ten is an inadequate number of subjects, particularly in a parallel trial. (4) The interpretation of the viscosity data was made using a method for which no details were provided. The "viscosity" of sputum was measured with a modified thromboelastograph. The details of the methodology were not provided, nor was the agency able to find any published material relating to that device. While the figures for the treated subjects appear to differ from those of the placebo group, they contain no explanations and no legends. Therefore, the agency has no basis to determine if the results using the modification are adequate or acceptable. (5) Adequate statistical evidence of effectiveness might have been provided from sputum volume and viscosity results had there been no missing data. Missing data were filled in by inserting the average value of the day immediately preceding or immediately following the missing data entry. This is not acceptable procedure.

In conclusion, Study 2 contains insufficient data and an inadequate number of subjects. The agency concludes that the submitted data are inadequate to include ipecac as an active ingredient in the final monograph for OTC expectorant drug products.

The agency's detailed comments on the data are on file in the Dockets Management Branch (address above) (Refs. 3 and 4).

References

(1) Comment No. CP, Docket No. 76N–052E, Dockets Management Branch, Study 1.

(2) Comment No. CP, Docket No. 76N–052E, Dockets Management Branch, Study 2.

(3) Letter from W. E. Gilbertson, FDA, to H. Jenkins, Creomulsion Co., coded PDN1, Docket No. 76N–052E, Dockets Management Branch.

(4) Letter from W. E. Gilbertson, FDA, to H. Jenkins, Creomulsion Co., coded LET089 Docket No. 76N–052E, Dockets Management Branch.

Therefore, the agency is amending 21 CFR 310.545 by adding new paragraphs (a)(6)(iii), (d)(4), and (d)(5) and by revising paragraph (d)(1) to establish that ipecac and certain other active ingredients are not generally recognized as safe and effective or are misbranded for OTC use in expectorant drug products.

The agency has determined that ipecac as an OTC expectorant drug active ingredient is not generally recognized as safe and effective. Therefore, ipecac as an expectorant ingredient for OTC use is considered a nonmonograph ingredient and misbranded under section 502 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 352) and is a new drug within the meaning of section 201(p) of the act (21 U.S.C. 321(p)) for which an approved application under section 505 of the act (21 U.S.C. 355) and part 314 of the regulations (21 CFR part 314) is required for marketing. In appropriate circumstances, a citizen petition to amend the monograph (21 CFR part 341) may be submitted in support of ipecac's use as an expectorant under 21 CFR 10.30 in lieu of an application. Any drug product containing ipecac as an expectorant active ingredient for OTC use initially introduced or initially delivered for introduction into interstate commerce or repackaged or relabeled after the effective date of this final rule is not in compliance with the regulation and is subject to regulatory action.

The agency has examined the economic consequences of this final rule in conjunction with other rules resulting from the OTC drug review. In a notice published in the **Federal Register** of February 8, 1983 (48 FR 5806), the agency announced the availability of an assessment of these economic impacts. The assessment determined that the combined impacts of all the rules resulting from the OTC drug review do not constitute a major rule according to the criteria established by Executive Order 12291. The agency therefore concludes that no one of these rules, including this final rule for OTC expectorant drug products, is a major rule.

The economic assessment also concluded that the overall OTC drug review was not likely to have a significant economic impact on a substantial number of small entities as defined in the Regulatory Flexibility Act (Pub. L. 96–354). That assessment included a discretionary regulatory flexibility analysis in the event that an individual rule might impose an unusual or disproportionate impact on small entities. However, this particular rulemaking for OTC expectorant drug products is not expected to pose such an impact on small businesses. This final rule only affects the status of ipecac as an OTC expectorant. There are only a limited number of OTC expectorant drug products that contain this ingredient. All of these products can be reformulated to contain guaifenesin, a monograph expectorant ingredient. For all other active ingredients listed in this final rule, the effective date (February 28, 1990) has already occurred. Therefore, the agency certifies that this final rule will not have a significant economic impact on a substantial number of small entities.

The agency has determined under 21 CFR 25.24(c)(6) 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.

List of Subjects in 21 CFR Part 310

Administrative practice and procedure, Drugs, Labeling, Medical devices, 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 310 is amended as follows:

PART 310—NEW DRUGS

1. The authority citation for 21 CFR part 310 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 512–516, 520, 601(a), 701, 704, 705, 706 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 360b–360f, 360j, 361(a), 371, 374, 375, 376); secs. 215, 301, 302(a), 351, 354–360F of the Public Health Service Act (42 U.S.C. 216, 241, 242(a), 262, 263b–263n).

2. Section 310.545 is amended by adding new paragraph (a)(6)(iii), by revising paragraphs (d) introductory text and (d)(1), and by adding new paragraphs (d)(4) and (d)(5), to read as follows:

§ 310.545 Drug products containing certain active ingredients offered over-the-counter (OTC) for certain uses.

(a) * * *

(6) * * *

(iii) *Expectorant drug products.*

Ammonium chloride
Antimony potassium tartrate
Beechwood creosote
Benzoin preparations (compound tincture of benzoin, tincture of benzoin)
Camphor
Chloroform
Eucalyptol/eucalyptus oil
Horehound
Iodides (calcium iodide anhydrous, hydriodic acid syrup, iodized lime, potassium iodide)
Ipecac
Ipecac fluidextract
Ipecac syrup
Menthol/peppermint oil
Pine tar preparations (extract white pine compound, pine tar, syrup of pine tar, compound white pine syrup, white pine)
Potassium guaiacolsulfonate
Sodium citrate
Squill preparations (squill, squill extract)
Terpin hydrate preparations (terpin hydrate, terpin hydrate elixir)
Tolu preparations (tolu, tolu balsam, tolu balsam tincture)

Turpentine oil (spirits of turpentine)

* * * * *

(d) Any OTC drug product that is not in compliance with this section is subject to regulatory action if initially introduced or initially delivered for introduction into interstate commerce after the dates specified in paragraphs (d)(1) through (d)(5) of this section.

(1) May 7, 1991, for products subject to paragraphs (a)(1) through (a)(6)(ii), and (a)(7) through (a)(19) of this section; and

* * * * *

(4) February 28, 1990, for products subject to paragraph (a)(6)(iii) of this section, except those that contain ipecac.

(5) September 14, 1993, for products subject to paragraph (a)(6)(iii) of this section that contain ipecac.

Dated: June 10, 1992.

Michael R. Taylor,

Deputy Commissioner for Policy.

[FR Doc. 92-22005 Filed 9-11-92; 8:45 am]

BILLING CODE 4160-01-F

21 CFR Part 522

Implantation or Injectable Dosage Form New Animal Drugs; Estradiol; Technical Amendment

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the animal drug regulations to reflect a technical amendment to the specifications and labeling of a new animal drug. The new animal drug application (NADA) for this new animal drug is sponsored by Elanco Animal Health, A Division of Eli Lilly & Co. The NADA provides for the veterinary use of estradiol (Compudose® 200 and 400) implants for steers and heifers.

EFFECTIVE DATE: September 14, 1992.

FOR FURTHER INFORMATION CONTACT: Russell G. Arnold, Center for Veterinary Medicine (HFV-142), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301-295-8674.

SUPPLEMENTARY INFORMATION: Elanco Animal Health, A Division of Eli Lilly & Co., Lilly Corporate Center, Indianapolis, IN 46285, is the sponsor of NADA 118-123, which provides for the use of an estradiol subcutaneous ear implant in steers and heifers. The NADA was approved on March 12, 1982 (47 FR 10805). A recalculation of the batch formulas used in manufacturing the implant revealed that the amount of estradiol in the product was incorrectly stated in the application. The estradiol content is 25.7 or 43.9 milligrams (mg) of estradiol, not the currently declared 24 or 45 mg. The amendment is approved as of May 4, 1992. The regulations are amended by revising 21 CFR 522.840(a), (c)(1), and (c)(3), accordingly, effective September 14, 1992.

This amendment represents a technical correction to the regulations and more accurately reflects the product specifications. Accordingly, a freedom of information summary as provided by 21 CFR 514.11(e)(2) is not required.

List of Subjects in 21 CFR Part 522

Animal drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs and redelegated to the Center for Veterinary Medicine, 21 CFR part 522 is amended as follows:

PART 522—IMPLANTATION OR INJECTABLE DOSAGE FORM NEW ANIMAL DRUGS

1. The authority citation for 21 CFR part 522 continues to read as follows:

Authority: Sec. 512 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360b).

§ 522.840 [Amended]

2. Section 522.840 Estradiol is amended in paragraphs (a), (c)(1), and (c)(3) by removing the numbers "24" and "45" and adding in their place "25.7" and "43.9", respectively.

Dated: September 3, 1992.

Gerald B. Guest,

Director, Center for Veterinary Medicine.

[FR Doc. 92-22077 Filed 9-11-92; 8:45 am]

BILLING CODE 4160-01-F

21 CFR Parts 522 and 556

Animal Drugs, Feeds, and Related Products; Ceftiofur

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the animal drug regulations to reflect approval of two supplemental new animal drug applications (NADA's) filed by The Upjohn Co. The supplements provide for the use of ceftiofur sterile powder for injection in swine for treatment and control of certain forms of swine bacterial respiratory disease and in day-old chicks for control of colibacillosis associated with *E. coli* sensitive to ceftiofur. The regulations are also amended to state that a tolerance for residues of ceftiofur in edible swine and chicken tissue derived from treated animals is not required.

EFFECTIVE DATE: September 14, 1992.

FOR FURTHER INFORMATION CONTACT: George K. Haibel, Center for Veterinary Medicine (HFV-133), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301-295-8644.

SUPPLEMENTARY INFORMATION: The Upjohn Co., Kalamazoo, MI 49001, is the sponsor of NADA 140-338 which provides for the use of Naxcel® Sterile Powder (ceftiofur sodium) as a 50 milligrams (mg) per milliliter reconstituted injectable. The original approval provided for intramuscular (IM) use to treat cattle (see 21 CFR 522.313). One supplement provides for IM use in swine at 3 to 5 mg per kilogram (1.36 to 2.27 mg per pound) of body weight for the treatment and control of bacterial respiratory disease. A second supplement provides for subcutaneous use in the neck of day-old chicks at 0.08 to 0.20 mg per chick for control of colibacillosis associated with *E. coli* sensitive to ceftiofur. The supplemental NADA's are approved as of August 4, 1992, and 21 CFR 522.313 is amended by adding new paragraphs (d)(2) and (d)(3) to reflect the approvals. The basis for approval is discussed in the freedom of information summary.

In addition, § 556.113 is amended to state that a tolerance for residues of ceftiofur in edible swine and chicken tissues derived from treated animals is not required.

In accordance with the freedom of information provisions of part 20 (21 CFR part 20) and § 514.11(e)(2)(ii) (21 CFR 514.11(e)(2)(ii)), a summary of safety and effectiveness data and information submitted to support approval of these supplements may be seen in the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857, between 9 a.m. and 4 p.m., Monday through Friday.

Under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360b(c)(2)(F)(iii)), these approvals qualify for 3 years of marketing exclusivity beginning August 4, 1992, because they contain reports of new clinical or field investigations and human food safety studies, other than bioequivalence or residue studies, essential to the approval and conducted or sponsored by the applicant.

The agency has carefully considered the potential environmental effects of this action. FDA has concluded that this action will not have a significant impact on the human environment, and that an