thereby engage in data processing activities, pursuant to § 225.25(b)(7) of the Board's Regulation Y. Specifically, ProImage, Inc., will provide check imaging and item processing services to banks.

B. Federal Reserve Bank of Minneapolis (James M. Lyon, Vice President) 250 Marquette Avenue, Minneapolis, Minnesota 55480:

*1. Norwest Corporation*, Minneapolis, Minnesota; to engage *de novo* through its subsidiary, Real Estate Financial, Palm Harbor, Florida, in a joint venture, and thereby engage in residential mortgage lending business, pursuant to § 225.25(b)(1) of the Board's Regulation Y. The co-venturers will be Norwest Ventures, Inc., and First in Real Estate Corporate Center, Inc., Palm Harbor, Florida.

Board of Governors of the Federal Reserve System, May 20, 1996.

Jennifer J. Johnson,

*Deputy Secretary of the Board.*

[FR Doc. 96–13135 Filed 5–23–96; 8:45 am]

**BILLING CODE 6210–01–F**

## Board of Governors; Sunshine Act Meeting Notice

**AGENCY HOLDING THE MEETING:** Board of Governors of the Federal Reserve System.

**TIME AND DATE:** 10:00 a.m., Wednesday, May 29, 1996.

**PLACE:** Marriner S. Eccles Federal Reserve Board Building, C Street entrance between 20th and 21st Streets, N.W., Washington, D.C. 20551.

**STATUS:** Closed.

**MATTERS TO BE CONSIDERED:**

1. Personnel actions (appointments, promotions, assignments, reassignments, and salary actions) involving individual Federal Reserve System employees.

2. Any items carried forward from a previously announced meeting.

**CONTACT PERSON FOR MORE INFORMATION:** Mr. Joseph R. Coyne, Assistant to the Board; (202) 452–3204. You may call (202) 452–3207, beginning at approximately 5 p.m. two business days before this meeting, for a recorded announcement of bank and bank holding company applications scheduled for the meeting.

Dated: May 22, 1996.

Jennifer J. Johnson,

*Deputy Secretary of the Board.*

[FR Doc. 96–13241 Filed 5–22–96; 10:16 am]

**BILLING CODE 6210–01–P**

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Office of the Secretary

### Agency Information Collection Activities: Submission for OMB Review; Comment Request

The Department of Health and Human Services, Office of the Secretary, publishes a list of information collections it has submitted to the Office of Management and Budget (OMB) for clearance in compliance with the Paperwork Reduction Act of 1995 (44 U.S.C. Chapter 35) and 5 CFR 1320.5. The following are those information collections recently submitted to OMB.

1. Alternative Models of Personal Assistance Services—NEW—The Office of the Assistant Secretary for Planning and Evaluation is planning a data collection which will compare modes of service delivery used to provide personal care services to the frail, elderly, and disabled persons of all ages. The three main provider modes to be compared are consumer-directed independent providers, supported independent providers, and contract or agency providers. The comparison is intended to further knowledge of the advantages and disadvantages of the alternative provider modes. Respondents: Individuals or households; state or local governments, business or other for-profit, not-for-profit institutions. Burden Information for Client Questionnaire—Responses: 1230; Burden per Response: 45 minutes; Total Burden: 923 hours—Burden for Provider Questionnaire—Responses: 530; Burden per Response: 40 minutes; Total Burden: 353 hours—Burden Information for Case Manager Questionnaire—Responses: 100; Burden per Response: 60 minutes; Total Burden: 100 hours—Burden Information for Client Qualitative Interview—Responses: 100; Burden per Response: 60 minutes; Total Burden: 100 hours—Burden Information for Provider Qualitative Interview—Responses: 150; Burden per Response: 55 minutes; Total Burden: 137 hours—Burden Information for Family Qualitative Interview—Responses: 150; Burden per Response: 45 minutes; Total Burden: 113 hours—Total Burden for Project: 1,726 hours.

OMB Desk Officer: Allison Eydt.

Copies of the information collection packages listed above can be obtained by calling the OS Reports Clearance Officer on (202) 690–6207. Written comments and recommendations for the proposed information collection should be sent directly to the OMB desk officer designated above at the following address: Human Resources and Housing Branch, Office of Management and Budget, New Executive Office Building, Room 10235, 725 17th Street N.W., Washington, D.C. 20503.

Comments may also be sent to Cynthia Agens Bauer, OS Reports Clearance Officer, Room 503H, Humphrey Building, 200 Independence Avenue S.W., Washington DC, 20201. Written comments should be received within 30 days of this notice.

Dated: May 15, 1996.

Dennis P. Williams,

*Deputy Assistant Secretary, Budget.*

[FR Doc. 96–13055 Filed 5–23–96; 8:45 am]

**BILLING CODE 4150–04–M**

## Food and Drug Administration

**[Docket No. 94D–0401]**

### Bioequivalence Guidance, 1996; Availability

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice.

**SUMMARY:** The Food and Drug Administration (FDA) is announcing the availability of the revised guidance document entitled ''Bioequivalence Guidance, 1996'' prepared by the Center for Veterinary Medicine (CVM). The availability of a draft guideline entitled ''Bioequivalence Guideline (Draft) 1994'' was announced in the Federal Register of March 1, 1995 (60 FR 11097) (hereinafter referred to as the 1994 draft guideline). The 1994 draft guideline was a revision of the 1990 version and covered the following areas: General considerations, blood level studies, pharmacologic endpoints, clinical endpoints, and human food safety. The guidance is intended to assist sponsors of new animal drug applications (NADA's) in the design and analysis of in vivo bioequivalence studies. This notice addresses comments submitted on the 1994 draft guideline.

**DATES:** Written comments on the guidance document may be submitted at any time.

**ADDRESSES:** Submit written requests for single copies of the guidance document entitled ''Bioequivalence Guidance, 1996'' to the Communications and Education Branch (HFV–12), Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301–594–1755. Send two self-addressed adhesive labels to assist that office in processing your requests. Submit written comments on the guidance document to the Dockets Management Branch (HFA–305), Food

and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857. Requests and comments should be identified with the docket number found in brackets in the heading of this document. A copy of the guidance document and received comments may be seen at the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

**FOR FURTHER INFORMATION CONTACT:** Melanie R. Berson, Center for Veterinary Medicine (HFV–135), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301–594–1643.

**SUPPLEMENTARY INFORMATION:** FDA is announcing the availability of the revised guidance entitled ''Bioequivalence Guidance, 1996''. The guidance may be used by sponsors of NADA's for the design and analysis of in vivo bioequivalence studies.

In a notice published in the Federal Register of March 1, 1995 (60 FR 11097), FDA announced the availability of the 1994 draft guideline entitled ''Bioequivalence Guideline (Draft) 1994''. The 1994 draft guideline was based on an April 1990 bioequivalence guidance and reports from panel presentations at the 1993 Veterinary Drug Bioequivalence Workshop held in Rockville, MD. New topics addressed in the 1994 draft guideline included: Bioequivalence overdose studies, testing for multiple strength solid oral dosage forms, assay considerations, area under the curve and maximum blood concentration as pivotal parameters, and blood level studies with good laboratory practice tissue residue depletion studies for generic products for food animals. Interested persons were given until May 30, 1995, to comment on the 1994 draft guideline.

Comments on the 1994 draft guideline were received from a pharmaceutical company and an industry group. The 1994 draft guideline has been revised as a result of these comments and from internal discussions within CVM. In the following section on received comments and CVM responses, the page numbers and sections refer to those found in the 1994 draft guideline.

1. Section II.E. Dose Selection. The comment objected to the use of the term ''overdose bioequivalence study'' since ''overdose'' has toxicological connotations.

CVM accepts the comments and will change the wording from ''overdose'' to ''higher than approved dose.''

2. Section II.F. Multiple Strengths of Solid Oral Dosage Forms. One comment asked for the rationale for requiring two bioequivalence studies in order to obtain approval when there are more than three strengths of exactly proportional formulations.

CVM accepts the comment and has modified the guidance to allow more flexibility in the determination of the need for more than one bioequivalence study for multiple strengths of solid oral dosage forms. The guidance has been modified to read as follows:

The generic sponsor should discuss with CVM the appropriate *in vivo* bioequivalence testing and *in vitro* dissolution testing to obtain approval for multiple strengths (or concentrations) of solid oral dosage forms.

CVM will consider the ratio of active to inactive ingredients and the *in vitro* dissolution profiles of the different strengths, the water solubility of the drug, and the range of strengths for which approval is sought.

One *in vivo* bioequivalence study with the highest strength product may suffice, if the multiple strength products have the same ratio of active to inactive ingredients and are otherwise identical in formulation.

*In vitro* dissolution testing should be conducted, using an FDA approved method, to compare each strength of the generic product to the corresponding strength of the reference product.

3. Section II.G. Manufacturing of Pilot Batch (''Biobatch''). One comment requested that terms such as 'pilot' and 'biobatch' need to be precisely defined in this document or reference made to the manufacturing guidelines.

CVM refers the reader to CVM's ''Animal Drug Manufacturing Guidelines, 1994'' for definition of terms.

4. Section III.A. Assay Considerations. One comment requests that CVM should adopt the same guidance as established in the joint industry/academia conference on ''Analytical Methods Validation: Bioavailability, Bioequivalence, and Pharmacokinetics Studies'' published in several journals including the *Journal of Pharmaceutical Sciences*, 81(3), 309–312, 1992.

CVM does not agree with this comment. The substance of CVM's guidance does not differ substantially from those used by CDER. Any difference is the result of CVM's interest in maintaining consistency among its analytical criteria for drug residues in the edible tissues. Drug residue measurement in edible tissues is specific to animal drugs and is not applicable to CDER (human drugs).

5. Section III.C.6.a. Area Under the Curve (AUC) Estimates. One comment questioned whether AUC by the linear trapezoidal rule is the preferred method to estimate AUC, and noted that the method is subject to substantial error when data points are widely spaced (e.g., during the terminal exponential disposition phase).

CVM accepts the comment and will modify the wording in the guidance to acknowledge that methods other than the linear trapezoidal rule may be used for estimating AUC, but the alternative method should be accompanied by appropriate references.

6. Section III.C.6.a. One comment questioned the reason to equate AUC over a dosing interval at steady-state to single-dose AUC zero to infinity. The comment stated that this relationship only holds if pharmacokinetics are linear over the relevant dose range and one of the prime reasons for doing a multiple-dose bioequivalence study is when kinetics are nonlinear.

CVM has modified the guidance to read as follows:

Under steady state conditions, $AUC_{0\text{-}t}$ equals the full extent of bioavailability of the individual dose ($AUC_{0\text{-}INF}$), assuming linear kinetics. For drugs which are known to follow nonlinear kinetics, the sponsor should consult with CVM to determine the appropriate parameters for the bioequivalence determination.

7. Section III.C.6.c. Determination of Product Bioequivalence. One comment requested that the sponsor should be allowed to extend the range of acceptable bioequivalence limits for drugs exhibiting highly variable pharmacokinetics, if adequate justification is provided.

CVM accepts the comment and has modified the guidance to include the following statement:

The sponsor and CVM should agree to the acceptable bounds for the confidence limits for the particular drug and formulation during protocol development. If studies or literature demonstrate that the pioneer drug product exhibits highly variable kinetics, then the generic drug sponsor may propose alternatives to the generally acceptable bounds for the confidence limits.

8. One comment requested that the repeated references to flip-flop kinetics should be replaced by the more general term ''prolonged absorption.''

CVM accepts the comment and has replaced the term ''flip-flop kinetics'' with ''sustained or prolonged absorption.''

9. One comment requested that the Bioequivalence Guidance provide more detail on evaluation of Production Drugs and Short Term Therapeutic Treatments in Feed (Staff Manual Guide 1240.4145).

CVM does not agree with the request to elaborate on combination drugs for use in feed. The focus of the Bioequivalence Guidance is the approval of generic animal drugs, although many of the principles may be applied to blood level studies conducted for other purposes. CVM considers it beyond the scope and intent of this guidance to discuss combination approvals for feeds.

10. Page 1, section I. INTRODUCTION, fifth paragraph. One

comment requested insertion of the following paragraph:

Tissue residue studies will not normally be required if blood concentration curve shape and depletion time through the reference product's withdrawal time are the same for generic and reference products. Tissue residue studies will normally be required where the blood levels cannot be measured prior to the elapse of the reference product's withdrawal period.

CVM does not agree with the change proposed by this comment. The pivotal parameters for the drug concentration versus time curve are AUC and $C_{MAX}$. CVM does not intend to evaluate curve shape and depletion time as pivotal parameters. For clarity, however, the guidance has been modified to read as follows:

The Center has concluded that the tissue residue depletion of the generic product is not adequately addressed through bioequivalence studies. Therefore, ANADA's for drug products for food-producing animals will generally be required to include bioequivalence and tissue residue studies. A tissue residue study will generally be required to accompany clinical end-point and pharmacologic end-point bioequivalence studies, and blood level bioequivalence studies that can not quantify the concentration of the drug in blood throughout the established withdrawal period.

11. Page 2, section II.A. Selection of Reference Product for Bioequivalence Testing, second paragraph. One comment suggested that the paragraph should read ''but remains eligible to be copied, then the first approved *and available* generic copy of the pioneer should be used * * *.''

CVM accepts the comment and has reworded the paragraph.

12. Page 5, first full paragraph. One comment suggests that multiple bioequivalence studies at different doses should only be required if the pharmacokinetics are not linear.

CVM accepts the recommendation and has modified the guidance to read as follows:

For products labeled for multiple claims involving different pharmacologic actions at a broad dose range (*e.g.*, therapeutic and production claims), a single bioequivalence study at the highest approved dose will usually be adequate. However, multiple bioequivalence studies at different doses may be needed if the drug is known to follow nonlinear kinetics. The sponsor should consult with CVM to discuss the bioequivalence study or studies appropriate to a particular drug.

13. Page 6, section III.A.1. Concentration Range and Linearity. One comment proposed that ''at least 5–8 concentrations'' is vague and suggested ''at least 5 concentrations.''

CVM accepts the comment and has changed the wording to ''at least 5 concentrations.''

14. Page 7, section III.A.4. Specificity. One comment requested that CVM provide further detail on statistical methods for demonstrating ''parallelism and superimposability.'' Analysis of variance is used to compare means but could be used to compare slopes in this case. This is computationally straightforward for linear curves but nonlinear curves (e.g., microbiological assays) pose unique problems.

CVM's response is that the type of statistical procedure used to process data demonstrating parallelism and superimposability of curves depends on the nature of the experimental data. CVM is allowing the sponsor the flexibility to determine the algorithm used to evaluate data. Whatever statistical procedure is used should be justified by the sponsor.

The use of microbiological assays for drug analysis will be addressed in a future CVM guidance.

15. Page 8, sections III.A.5. Accuracy (Recovery) and III.A.6. Precision. One comment requested that ''replicate injections'' be changed to ''replicates.''

CVM accepts the comment.

16. Page 8, section III.A.6. Precision. One comment stated that the suggested coefficient of variation of ± 10 percent for concentrations at or above 0.1 micrograms per milliliter (mL) is too stringent. The comment suggested ±15 percent as an alternative coefficient of variation to target.

CVM does not agree with this comment. In light of today's analytical technology, ±10 percent coefficient of variation is not unreasonable and is consistent with CVM policy in other analytical areas. In addition, CVM does not believe anything is gained by a detailed analysis of the sources of variation in analytical results.

17. Page 8, section III.A.7. Analyte Stability, second paragraph. One comment recommended that stability samples at only two concentrations are necessary, rather than three as suggested in the 1994 draft guideline. It is critically important to validate the assay before conduct of the bioequivalence study. However, analyte stability cannot be done without the use of more animals than required by the bioequivalence study so as to have a valid method in place prior to study initiation. It is impossible to store and begin analyzing stability samples throughout the duration of the bioequivalence study analysis phase unless the method has been validated prior to that study's initiation.

CVM does not agree with this comment. No study should be undertaken until the analytical methods that will be used to develop the data are properly validated and shown to be operating in a state of control in the laboratory. This means that after the method is validated, the laboratory intending to use the method for a study, must practice with the method to assure full familiarization with technical details. CVM does not make any recommendation on how much practice is required. This depends on the complexity of the method and on the experience of the laboratory.

18. Page 8, section III.A.8. Analytical System Stability. One comment stated that it was unclear how the use of standards (of multiple concentrations) repetitively run to assure analytical system stability differs from quality control methods of assuring the same thing.

CVM accepts the comment that the wording on the use of standards may be unclear. The guidance section on ''Assay Considerations'' has been extensively reworded for clarity.

19. Page 9, section III.B.1. Dosing by Labeled Concentration. One comment asked how the assay prior to study will be used to ensure specifications. What actions can the sponsor take if the pioneer assays at -5 percent while the generic assays at +5 percent.

CVM's response is that the pioneer and generic products should be assayed to determine that the particular lots are within specifications. No action can be taken if the pioneer assays at -5 percent while the generic assays at +5 percent.

For clarity, the guidance has been reworded to read as follows: ''To maximize the ability to demonstrate bioequivalence, the Center recommends that the potency of the pioneer and generic lots should differ by no more than ±5% for dosage form products.''

20. Page 10, section III.B.2. Single Dose vs Multiple Dose Studies. One comment questioned whether documentation of flip-flop kinetics is necessary.

CVM agrees with this comment and has modified the guidance to read as follows:

A multiple dose study may also be needed when assay sensitivity is inadequate to permit drug quantitation out to 3 terminal elimination half-lives beyond the time when maximum blood concentrations ($C_{max}$) are achieved, or in cases where prolonged or delayed absorption[2] exist. The determination of prolonged or delayed absorption (*i.e.*, flip-flop kinetics) may be made from pilot data, from the literature, or from the CVM database on the particular drug or family of drugs.

21. Page 11, section III.B.4. Fed vs Fasted State, last paragraph. One comment stated that it was unclear whether studies in both the fed and fasted states should be required for enteric-coated or sustained release oral

products. If the referenced product is limited to administration either in the fed or the fasted state, then the test formulation should also be administered in the same situation conforming to the reference product's label.

CVM agrees with this comment and has modified the guidance as follows:

If a pioneer product label indicates that the product is limited to administration either in the fed or fasted state, then the bioequivalence study should be conducted accordingly. If the bioequivalence study parameters pass the agreed upon confidence intervals, then the single study is acceptable as the basis for approval of the generic product.

However, for certain product classifications or drug entities, such as enteric coated and oral sustained release products, demonstration of bioequivalence in both the fasted and fed states may be necessary, if the drug is highly variable under feeding conditions, as determined from the literature or from pilot data. A bioequivalence study conducted under fasted conditions may be necessary to pass the confidence intervals. A second smaller study may be necessary to examine meal effects. CVM will evaluate the smaller study with respect to the means of the pivotal parameters (AUC, $C_{MAX}$). The sponsor should consult with CVM prior to conducting the studies.

22. Page 12, section III.C.2. Protein Binding. One comment stated that it is not clear from the 1994 draft guideline to what extent the protein binding must be nonlinear within the therapeutic dosing range, nor how determination of linearity is to be conducted. If it is a judgment and not a statistical criterion, then the parameters within which that judgment is made need to be determined prior to embarking upon the abbreviated NADA. In addition, the type of blood protein to which the drug binds is only pertinent in very unique situations (i.e., low capacity protein binding situations). These determinations of the type of blood protein to which the drug binds are very tedious, time-consuming and expensive technical studies that may only rarely be relevant, whereas the magnitude of protein binding is critical. The type of blood protein to which the drug binds is only a consideration if prior data indicate it is a concern. There are numerous instances where CVM requires additional studies ''if ———————— is known to occur.'' What are the criteria for knowing? This general statement could lead to intractable situations. Specifically for this section, the wording allows CVM to require protein binding studies for all approvals. A proposal would be to first evaluate the blood profiles observed in the pilot studies to see if there is evidence of such binding (multicompartment phenomena). If not, then eliminate the need for further studies. For combination approvals, the necessary fractionation and assessment of matrix effects using micro methods would be a formidable task.

CVM notes that the Bioequivalence Guidance is not intended to address combination drug approvals. The issue of protein binding for generic approvals would be addressed only if literature or pilot data indicate that protein binding is significant to the drug in question. For clarity, however, the guidance has been modified to read as follows:

However, if nonlinear protein binding is known to occur within the therapeutic dosing range (as determined from literature or pilot data), then sponsors may need to submit data on both the free and total drug concentrations for the generic and pioneer products.

23. Page 14, section III.C.4. Cross-over and Parallel Design Considerations, last sentence. One comment proposed that the pilot data be used in support of alternative study designs during discussions with CVM.

CVM agrees with the comment. The guidance statement has been modified to read as follows: ''The use of alternative study designs should be discussed with CVM prior to conducting the bioequivalence study. Pilot data or literature may be used in support of alternative study designs.''

24. Page 15, top paragraph. One comment regarding the duration of washout time was that prolonged tissue binding may not be a consequence if drug concentrations in plasma are less than the limit of detection. The onus is on the sponsor for having a sufficiently long washout period to allow the second period of the cross-over study to be applicable in the statistical analysis. If sequence effects are noted, it must be emphasized that at the very minimum the same data from the first period alone can be evaluated as a parallel design study.

CVM agrees with the comments and has modified the paragraph in the guidance to read as follows:

The washout period should be sufficiently long to allow the second period of the cross-over study to be applicable in the statistical analysis. However, if sequence effects are noted, the data from the first period may be evaluated as a parallel design study.

25. Page 15, section III.C.6.a., AUC Estimate. One comment stated that it is implied from the discussions regarding AUC and $C_{MAX}$ that ratio testing (the ratio of the test versus the reference product) is considered to be the more appropriate comparison rather than the difference between the test and the reference product. This is not universally accepted as the case. The responsibility for whether the difference between the two is used or the ratio of the two is used should be placed upon the sponsor and should be concurred with by CVM prior to conduct of the study.

CVM does not agree with nor completely understand the comment's interpretation of the guidance. CVM has, however, changed the word ''ratio'' to ''comparison'' in the following sentence:

The comparison of the test and reference product value for this noninfinity estimate provides the closest approximation of the measure of uncertainty (variance) and the relative bioavailability estimate associated with $AUC_{0\text{-}INF}$, the full extent of product bioavailability.

26. Page 15, section III.C.6.a. One comment stated that $AUC_{0\text{-}INF}$ is an estimated value and questioned how CVM intends this to be derived using ''model independent methods?''

CVM has added the following statement to the guidance: ''The method for estimating the terminal elimination phase should be described in the protocol and the final study report.''

27. Page 16, section III.C.6.b. Rate of Absorption. One comment requested that the revised guidance define $C_{MIN}$. The 1994 draft guideline stated that three successive $C_{MIN}$ values should be provided. The comment proposes that to determine a steady state concentration, the values should be regressed over time and the resultant slope should be tested as being different from zero.

CVM agrees with the comment and has modified the guidance to read as follows:

When conducting a steady-state investigation, data on the minimum drug concentrations (trough values) observed during a single dosing interval ($C_{MIN}$) should also be collected. Generally, three successive $C_{MIN}$ values should be provided to verify that steady-state conditions have been achieved. Although $C_{MIN}$ most frequently occurs immediately prior to the next successive dose, situations do occur with $C_{MIN}$ observed subsequent to dosing. To determine a steady state concentration, the $C_{MIN}$ values should be regressed over time and the resultant slope should be tested for its difference from zero.

28. Page 16, section III.C.6.c. Determination of Product Bioequivalence. One comment states that for multiple dose studies, $C_{MAX}$ and $AUC_{O\text{-}t}$ are applicable only if done at steady state. It is not clear from the current description that these must be steady state values to have the appropriate interpretation for bioequivalence testing.

CVM does not agree with the comment because a multiple dose bioequivalence study could be conducted with a drug that never achieves steady-state. However, the pioneer and generic products $C_{MAX}$ and

$AUC_{O-t}$ should be equivalent at any dosing interval whether or not steady-state is achieved.

29. Page 17, section III.D. Statistical Analysis, second paragraph. The choice of whether to use untransformed data should be made by the sponsor based on whether transformation is necessary to allow for homogeneity of variance. It should not be determined prior to the study because the data should dictate which transformation, if any, is required.

CVM does not agree with this recommendation. The sponsor has the option to use untransformed or log transformed data, but the decision should be made prior to conducting the study.

30. Page 19, section III.D., second from the last paragraph relating to selection of confidence interval. One comment noted that CVM states that in general the confidence interval for untransformed data should be 80 to 120. Firstly, percent should be specified. Secondly, emphasis should be added that these are general rather than the adamant and steadfast specifications of CVM. The opinion of many statisticians with considerable experience in this field is that the ±20 percent interval is entirely too restrictive. In the animal health market, the potential cost to evaluate generics or combinations may be so great as to preclude bringing a useful drug/combination to the market.

CVM has made the requested editorial changes. However, CVM will continue to accept ±20 percent as the acceptable confidence interval for the pivotal parameters. CVM invites sponsors to submit data to justify broadening the confidence interval for a particular drug.

31. Page 20, section IV.B. Statistical Analysis. One comment noted that for pharmacologic endpoint studies as described, it appears that these studies described are evaluating significant differences rather than statistical equivalence. As such, these pharmacological endpoint studies are not as rigorously designed from a statistical standpoint as classic bioequivalence plasma level studies, inasmuch as differences are being evaluated rather than equivalence. The comment suggested that pharmacological endpoint studies should also be evaluating statistical equivalence, rather than significant differences. In fact, a comparable equivalence testing is alluded to on page 22 regarding clinical endpoint studies, studies which would be expected to be less able to prove equivalence than pharmacologic endpoint studies.

CVM agrees with the comment and has modified the guidance to read as follows:

For parameters which can be measured over time, a time *vs* effect profile is generated, and equivalence is determined with the method of statistical analysis essentially the same as for the blood level bioequivalence study.

For pharmacologic effects for which effect vs time curves can not be generated, then alternative procedures for statistical analysis should be discussed with CVM prior to conducting the study.

32. Page 23, section VI. Human Food Safety Considerations. One comment asked if there is a need for determining a full depletion profile for the generic? The sponsor proposed that a single point tissue residue study completed out to the withdrawal time of the pioneer would be sufficient.

The Center does not agree with the use of a single point tissue residue study at the withdrawal time of the pioneer as a general practice.

A traditional tissue residue depletion study has always been required for generic products where bioequivalence is determined with a pharmacological or clinical endpoint study. The need for a traditional tissue residue depletion profile is expanded in the revised guidance to include blood level bioequivalence studies, because the Center has concluded that, with the exception of those examples listed in section VI. of the guidance, the tissue residue depletion of the generic product is not adequately addressed through bioequivalence studies.

The use of the traditional tissue residue depletion study provides the Center with the data needed to compute a withdrawal period for the drug product in question, using our statistical tolerance limit model, whereby the 99th percentile is calculated with 95 percent confidence. Use of a single point tissue residue study ordinarily would not provide the data needed to use our current model, since the single-point study would not contain sufficient information regarding the variability of the residue depletion profile. Additionally, since the analytical methods approved for regulatory purposes can rarely measure the marker residue at the withdrawal time, a single point residue study at the pioneer withdrawal time would be limited by the efficiency of the regulatory analytical method at the drug concentrations typically seen at the pioneer withdrawal time. When the tissue residue values include negative or zero values (i.e., values below the limit of quantitation for the assay), the number of animals needed in the study will depend on the method variance and the number of zero values, and will vary from drug to drug. It is not possible to predict, a priori, the number of animals that will be needed to provide data of sufficient confidence for a single point tissue residue depletion study to obtain the confidence similar to that seen for the pioneer drug using our traditional residue depletion study design.

The Center will consider the use of a single point tissue residue depletion study in those cases where the regulatory analytical method can be validated and demonstrated to measure reliably residues in the treated animals at the pioneer withdrawal time so that a 99th percentile statistical tolerance limit with 95 percent confidence can be calculated.

A person may follow the guidance or may choose to follow alternate procedures or practices. If a person chooses to use alternate procedures or practices, that person may wish to discuss the matter further with the agency to prevent an expenditure of money and effort on activities that may later be determined to be unacceptable to FDA. Although this guidance document does not bind the agency or the public, and it does not create or confer any rights, privileges, or benefits for or on any person, it represents FDA's current thinking on bioequivalence testing for animal drugs. When a guidance document states a requirement imposed by statute or regulation, the requirement is law and its force and effect are not changed in any way by virtue of its inclusion in the guidance.

Interested persons may, at any time, submit to the Dockets Management Branch (address above) written comments on the document. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. The documents and received comments are available for public examination in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

Dated: May 17, 1996.

William K. Hubbard,

*Associate Commissioner for Policy Coordination.*

[FR Doc. 96–13106 Filed 5–23–96; 8:45 am]

BILLING CODE 4160–01–F