inspection certificate, except when relieved from such requirements pursuant to §§ 956.63 or 956.64, or both. Upon recommendation of the committee, with approval of the Secretary, inspection providers and certification requirements may be modified to facilitate the handling of Walla Walla Sweet Onions.

(b) Regrading, resorting, or repacking any lot of Walla Walla Sweet Onions shall invalidate prior inspection certificates insofar as the requirements of this section are concerned. No handler shall ship Walla Walla Sweet Onions after they have been regraded, resorted, repacked, or in any other way further prepared for market, unless such onions are inspected by an authorized representative of the Federal-State Inspection Service, or such other inspection service as the Secretary shall designate: *Provided*, That such inspection requirements on regraded, resorted, or repacked Walla Walla Sweet Onions may be modified, suspended, or terminated under rules and regulations recommended by the committee, and approved by the Secretary.

(c) Upon recommendation of the committee, and approval of the Secretary, all Walla Walla Sweet Onions that are required to be inspected and certified in accordance with this section shall be identified by appropriate seals, stamps, tags, or other identification to be furnished by the committee and affixed to the containers by the handler under the direction and supervision of the Federal-State or Federal inspector, or the committee. Master containers may bear the identification instead of the individual containers within said master container.

(d) Insofar as the requirements of this section are concerned, the length of time for which an inspection certificate is valid may be established by the committee with the approval of the Secretary.

(e) When Walla Walla Sweet Onions are inspected in accordance with the requirements of this section, a copy of each inspection certificate issued shall be made available to the committee by the inspection service.

(f) The committee may enter into an agreement with an inspection service with respect to the costs of the inspection as provided by paragraph (a) of this section, and may collect from handlers their respective pro rata shares of such costs.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 314 and 320

[Docket No. 98N–0778]

Bioavailability and Bioequivalence Requirements; Abbreviated Applications; Proposed Revisions

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to revise its regulations on bioavailability and bioequivalence and on the content and format of an abbreviated application to reflect current FDA policy and to correct certain typographical and inadvertent errors. This action is intended to improve the accuracy and clarity of the regulations.

DATES: Written comments by February 2, 1999. FDA proposes that any final rule based on this proposal become effective 60 days after its date of publication in the **Federal Register**.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Christine F. Rogers, Center for Drug Evaluation and Research (HFD–7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–2041.

SUPPLEMENTARY INFORMATION:

I. Background

FDA regulations require persons submitting a new drug application (NDA) to provide bioavailability information (21 CFR 314.50(c)(2)(vi) and (d)(3)), and persons submitting an abbreviated new drug application (ANDA) or abbreviated antibiotic application (AADA) to provide information pertaining to bioavailability and bioequivalence (§ 314.94(a)(7) and (d)(3) (21 CFR 314.94(a)(7) and (d)(3))).

FDA regulations in part 320 (21 CFR part 320) establish definitions and requirements for bioavailability and bioequivalence studies. FDA finalized the bioavailability and bioequivalence regulations on January 7, 1977 (42 FR 1624), and amended these regulations on April 28, 1992 (57 FR 17950). The 1992 amendments were designed to reflect statutory changes resulting from the Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98–417).

Bioavailability, in general, refers to the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action (§ 320.1(a)). Bioequivalence, in general, refers to the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study. Where there is an intentional difference in rate (e.g., in certain controlled release dosage forms), certain pharmaceutical equivalents or alternatives may be considered bioequivalent if there is no significant difference in the extent to which the active ingredient or moiety from each product becomes available at the site of drug action (§ 320.1(e)).

II. Description of the Proposed Rule

The proposed rule would revise FDA regulations pertaining to abbreviated applications, bioavailability, and bioequivalence to reflect current agency policy, to correct typographical and inadvertent errors, and to clarify existing provisions. The proposed amendments follow.

Section 314.94(a)(9) establishes information requirements for the chemistry, manufacturing, and controls section of an abbreviated application. Section 314.94(a)(9) provides that an abbreviated application may have different inactive ingredients than the reference listed drug as long as the applicant identifies and characterizes the inactive ingredients in the proposed drug product and provides information demonstrating that the inactive ingredients do not affect the safety of the drug product. The proposed rule would amend this section to recognize the possibility that the use of different inactive ingredients may also affect a product's efficacy.

Section 314.94(a)(9)(v) establishes the requirements for inactive ingredient changes permitted in drug products intended for topical use. The proposed rule would revise this section to include solutions for aerosolization or nebulization as well as nasal solutions. This change is intended to clarify that these solutions may be characterized as drug products intended for topical use.

Section 314.127 (21 CFR 314.127) sets forth the reasons why FDA would refuse to approve an ANDA. The proposed rule would revise § 314.127(a)(8) to clarify that, consistent with current FDA policy, the applicant must show that different inactive ingredients would not affect a product's efficacy, in addition to the currently required showing for safety. This revision is necessary because a change in inactive ingredients may affect safety or efficacy or both. As the agency stated in the preamble to the proposed rule implementing the Drug Price Competition and Patent Term Restoration Act of 1984, ''[i]t is well established that changing the inactive ingredients in a drug can adversely affect the drug's safety or effectiveness.'' (See 54 FR 28872 at 28902, July 10, 1989.) For example, an inactive ingredient that increases or decreases an active ingredient's efficacy may affect the safety of the drug product as well. If a drug is not achieving its therapeutic purpose, the drug may be unsafe for use. An ineffective drug may cause a patient to unwittingly delay effective treatment. Thus, safety and effectiveness are, to a great extent, intertwining principles.

Section 320.1(c) defines ''pharmaceutical equivalents'' as:

* * * drug products that contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, in identical dosage forms, but not necessarily containing the same inactive ingredients, and that meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates.

This definition has been the source of some confusion with regard to certain modified release systems, prefilled syringes, and other drug products that contain a reservoir that facilitates delivery or where residual volume may vary. In such products, the agency does not consider the amount that facilitates the action of the delivery system, but by design is not intended to be delivered to the site of drug action or to have any direct therapeutic effect, to be ''active ingredient'' for the purposes of evaluating the pharmaceutical equivalence of a drug product.

Therefore, to clarify the definition of ''pharmaceutical equivalents'' with regard to certain drug products such as prefilled syringes and those that use modified release systems, the agency is proposing to revise the definition of ''pharmaceutical equivalents'' in § 320.1(c) to state:

* * * drug products in identical dosage forms that contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; do not necessarily contain the same inactive ingredients; and meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.

Subpart B of part 320 describes procedures for determining the bioavailability or bioequivalence of drug products, and refers to evidence that ''demonstrates'' in vivo bioavailability and bioequivalence. The proposed rule would modify current §§ 320.21, 320.22, 320.23, 320.24, and 320.25 to clarify that although bioequivalence may be ''demonstrated'' or ''established,'' bioavailability can only be ''measured.'' These verb changes also require that the words ''in vivo'' precede the word ''bioequivalence.''

Section 320.21 sets forth the requirements for submission of in vivo bioavailability and bioequivalence data. Section 320.21(b)(1) provides that any person submitting an abbreviated application must submit evidence demonstrating that the proposed drug product is bioequivalent to the reference listed drug or, under § 320.21(b)(2), provide ''[i]nformation to show that the drug product is bioequivalent to the reference listed drug which would permit FDA to waive the submission of evidence demonstrating bioequivalence * * *.'' The proposed rule would revise § 320.21(b)(2) to clarify that the waiver would only pertain to the submission of evidence demonstrating the in vivo determination of bioequivalence.

Section 320.21(c)(1) provides that any person submitting a supplemental application to FDA must provide evidence or information regarding the product's bioavailability or bioequivalence if the supplemental application proposes ''[a] change in the manufacturing process, including a change in product formulation or dosage strength, beyond the variations provided for in the approved application.'' The proposed rule would amend this provision to include a change in the manufacturing site because such a change may affect the bioavailability or bioequivalence of the drug product because of equipment, personnel, or environmental changes.

Section 320.21(d) states that ''FDA may approve a full new drug application * * * that does not contain evidence of in vivo bioavailability or information to permit waiver of the requirement for in vivo bioavailability data,'' if, among other things, ''[t]he application was under review by FDA on July 7, 1977'' (§ 320.21(d)(1).) The agency is proposing to remove this paragraph because it has become outdated.

Section 320.21(f) inaccurately includes a reference to criteria set forth in § 320.24 as containing information under which FDA could waive the requirement for submission of evidence demonstrating in vivo bioavailability or bioequivalence. The proposed rule would replace the reference to § 320.24 with § 320.22.

Proposed § 320.22(a) would address another typographical error. Current § 320.22(a) states that ''[e]xcept as provided in paragraph (g) of this section,'' FDA shall waive the requirement for the submission of evidence of in vivo bioavailability or bioequivalence under certain conditions. The proposed rule would substitute paragraph (f) for the reference to paragraph (g).

Section 320.22(b) sets forth the criteria under which a drug product's in vivo bioavailability or bioequivalence may be considered self-evident based on other data in an application showing that the proposed drug product is identical in certain respects to the ''drug product that is the subject of an approved full new drug application'' (see § 320.22(b)(1)(ii), (b)(2)(ii), and (b)(3)(ii)). The proposed rule would replace ''approved full new drug application'' with ''approved full new drug application or abbreviated new drug application.'' This revision recognizes those instances when an approved abbreviated new drug application might be the reference listed drug because there is no approved full new drug application. The proposed rule would make a similar change to § 320.22(b)(3)(iii) because this provision also refers to a ''drug product that is the subject of the approved full new drug application * * *.''

Section 320.22(b)(3)(i) sets forth the criteria for waiver of the in vivo bioavailability or bioequivalence of a drug product that is ''a solution for application to the skin, an oral solution, elixir, syrup, tincture, or similar other solubilized form'' intended for either local or systemic effect. The proposed rule would amend § 320.22(b)(3)(i) to include a ''solution for aerosolization or nebulization'' and a ''nasal solution'' to clarify that ''similar other solubilized form'' includes solutions for aerosolization or nebulization and nasal solutions.

Section 320.22(c) provides that ''FDA shall waive the requirement for the submission of evidence demonstrating

the in vivo bioavailability of a solid oral dosage form (other than an enteric coated or controlled release dosage form) * * *'' unless, among other things, ''FDA has evaluated the drug product under the criteria set forth in § 320.32 * * *.'' The reference to § 320.32 is a typographical error. The proposed rule would refer to § 320.33 because the relevant criteria are found in that provision. In addition, the proposed rule would clarify that FDA may waive this requirement not only for the submission of evidence of in vivo bioavailability but also for the submission of evidence of in vivo bioequivalence.

The proposed rule would also amend § 320.22(c) because ''delayed release'' is the preferred terminology for ''enteric coated'' and ''extended release'' is the preferred terminology for ''controlled release.''

Under § 320.22(e), ''FDA, for good cause, may waive a requirement for the submission of evidence of in vivo bioavailability if waiver is compatible with the protection of the public health * * *.'' When the agency revised and finalized the regulations in 1992, it intended that § 320.22(e) clearly include waiver of in vivo bioequivalence testing, as the heading of the section suggests. Indeed, waiver of the submission of in vivo bioavailability data is related to waiver of in vivo bioequivalence testing in that bioequivalence is an assessment of comparative bioavailability. Because there may be some confusion about the scope of § 320.22(e), the proposed rule would clarify that FDA may, for good cause, waive not only the submission of evidence of in vivo bioavailability but also the submission of evidence of in vivo bioequivalence, if such a waiver is compatible with the protection of the public health. Such a waiver may be appropriate in cases where an abbreviated application uses inactive ingredients different from those in the reference listed drug (see § 314.94(a)(9)), and thus the other provisions regarding a waiver of a the requirement for the submission of evidence of in vivo bioavailability or bioequivalence do not apply. In such cases, a waiver of the submission of evidence of in vivo bioavailability or bioequivalence may, for good cause, be granted if compatible with the protection of the public health.

Section 320.24 sets forth the various types of evidence needed to establish bioavailability or bioequivalence. The agency is removing § 320.24(b)(1)(iii) because FDA does not encourage the use of animals in vivo bioavailability studies. Section 320.24(b)(5), which focuses on one method, in vitro testing, contains a typographical error, stating that the in vitro test acceptable to FDA is ''unusually a dissolution rate test.'' The proposed rule would replace ''unusually'' with ''usually.''

Section 320.25 provides guidelines for the conduct of an in vivo bioavailability study. Section 320.25(a)(2) provides that ''[a]n in vivo bioavailability study shall not be conducted in humans if an appropriate animal model exists and correlation of results in animals and humans has been demonstrated * * *.'' The agency is proposing to remove § 320.25(a)(2) because FDA does not encourage the use of animals in vivo bioavailability studies.

Section 320.25(d)(1) describes the purpose of a bioavailability study involving a drug product containing an active drug ingredient or therapeutic moiety that has not been approved for marketing. The agency has determined that § 320.25(d)(1) is inaccurate because it actually describes the purpose of a pharmacokinetic study, rather than a bioavailability study. Thus, the proposed rule would revise the introductory text of § 320.25(d)(1) to read ''An in vivo bioavailability study involving a drug product containing an active drug ingredient or therapeutic moiety that has not been approved for marketing can be used to measure the following pharmacokinetic data: * * *.''

Section 320.25(e)(1) describes the purpose of an in vivo bioavailability study involving a drug product that is a new formulation, a new dosage form, or a new salt or ester of an active drug ingredient or therapeutic moiety that has been approved for marketing. The agency has determined that § 320.25(e)(1) is inaccurate because it also describes the purpose of a pharmacokinetic study, not a bioavailability study. Thus, the proposed rule would revise the introductory text of § 320.25(e)(1) to read ''An in vivo bioavailability study involving a drug product that is a new formulation, a new dosage form, or a new salt or ester of an active drug ingredient or therapeutic moiety that has been approved for marketing can be used to: * * *.''

Section 320.26 provides guidance on the design of a single-dose in vivo bioavailability study, and § 320.27 provides guidance on the design of a multiple-dose in vivo bioavailability study. The proposed rule would add the word ''bioequivalence'' after ''bioavailability'' throughout these two sections because §§ 320.26 and 320.27 are also applicable to in vivo bioequivalence studies. This revision reflects current FDA policy. The proposed rule would also amend §§ 320.28 and 320.29 to include reference to bioequivalence because these sections are also applicable to in vivo bioequivalence studies.

The proposed rule would also amend § 320.26(b)(2)(i) by replacing ''three'' with ''five.'' The proposed rule would also insert the word ''active'' before ''metabolite(s)'' in §§ 320.26(b)(2)(i) and 320.27(b)(3)(i). FDA is proposing these revisions because the drug elimination period (wash-out period) of three times the half-life of the active drug ingredient or therapeutic moiety, or its active metabolite(s), is inadequate, and because current analytical methods exist that usually are capable of detecting drug concentrations after five times the half-life of the active drug ingredient or therapeutic moiety, or its active metabolite(s).

Section 320.27(d)(1) states that, for the collection of blood samples during multiple-dose in vivo bioavailability studies, the maximum (Cmax) and minimum (Cmin) values should be defined on 2 or more consecutive days to establish that steady-state conditions are achieved. FDA no longer uses Cmax values in the determination of steady-state conditions and, in some cases, the predose trough level may not be the observed Cmin value. In addition, FDA recommends that sampling be done for at least 3 consecutive days. Therefore, the proposed rule would revise § 320.27(d)(1) to state:

> Whenever comparison of the test product and the reference material is to be based on blood concentration-time curves at steady-state, sufficient samples of blood should be taken to define adequately the predose blood concentration on 3 or more consecutive days to establish that steady-state conditions are achieved.

Section 320.27(d)(2) states that ''[w]henever comparison of the test product and the reference material is to be based on cumulative urinary excretion-time curves at steady-state, sufficient samples of urine should be taken to define the rate and extent of urinary excretion on 2 or more consecutive days to establish that steady-state conditions are achieved.'' For the reasons stated previously, the proposed rule would revise this paragraph to state:

> Whenever comparison of the test product and the reference material is to be based on cumulative urinary excretion-time curves at steady-state, sufficient samples of urine should be taken to define the rate and extent of urinary excretion on 3 or more consecutive days to establish that steady-state conditions are achieved.

Section 320.30(c)(1) directs inquiries on bioavailability to the Division of Biopharmaceutics in the Center for Drug Evaluation and Research. The proposal

would update the name of the Division of Biopharmaceutics because it is now called the ''Office of Clinical Pharmacology and Biopharmaceutics'' (HFD–850).

Section 320.30(c)(2) directs inquiries on bioequivalence requirements and methodology to the Division of Bioequivalence in the Center for Drug Evaluation and Research. The proposal would update the mailing address for the Division of Bioequivalence because it is now located at Metro Park North II, 7500 Standish Pl., Rockville, MD 20855–2773.

Section 320.31 discusses the applicability of the investigational new drug application requirements to certain bioavailability or bioequivalence studies. Although FDA intended that this section apply to bioavailability or bioequivalence studies, § 320.31(b) only refers to bioavailability studies. The proposal would insert the words ''or bioequivalence'' after the word ''bioavailability'' in the introductory text of § 320.31(b) to clarify that this section applies to bioequivalence studies as well.

Broader issues concerning FDA's interpretation and application of the regulations applicable to bioequivalence issues have recently been the subject of controversy. The ability to characterize and quantify the components of drug products has evolved and continues to evolve with advances in the science of analytical chemistry. A more refined characterization of a drug product may complicate determinations about the components or quantity of components that may affect the safety of the drug product or contribute to its pharmacological effect. Changes to definitional concepts such as active and inactive ingredients are beyond the scope of these, for the most part, technical revisions to the regulations. However, FDA intends to address such issues in a future proposal.

III. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612). 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). Under the Regulatory Flexibility Act, unless an agency certifies that a rule will not have a significant impact on small entities, the agency must analyze regulatory options that would minimize the impact of the rule on small entities. Title II of the Unfunded Mandates Reform Act (Pub. L. 104–114) (in section 202) requires that agencies prepare an assessment of anticipated costs and benefits before proposing any rule that may result in an expenditure in any 1 year by State, local, and tribal governments, in the aggregate, or by the private sector, of $100 million or more (adjusted annually for inflation).

The agency has reviewed this proposed rule and has determined that it is consistent with the regulatory philosophy and principles identified in Executive Order 12866, and these two statutes. With respect to the Regulatory Flexibility Act, the agency certifies that the rule will not have a significant economic impact on a substantial number of small entities. Because the proposed rule does not impose any mandates on State, local, or tribal governments, or the private sector that will result in a 1-year expenditure of $100 million or more, FDA is not required to perform a cost-benefit analysis under the Unfunded Mandates Reform Act.

The proposed rule would amend the bioavailability and bioequivalence regulations to reflect current FDA policy.

IV. Paperwork Reduction Act of 1995

FDA tentatively concludes that this proposed rule contains no collections of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

V. Environmental Impact

The agency has 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.

VI. Request for Comments

Interested persons may, on or before February 2, 1999, submit to the Dockets Management Branch (address above) written comments regarding this proposal. 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. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects

21 CFR Part 314

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

21 CFR Part 320

Drugs, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR parts 314 and 320 be amended as follows:

PART 314—APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG OR AN ANTIBIOTIC DRUG

1. The authority citation for 21 CFR part 314 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 357, 371, 374, 379e.

2. Section 314.94 is amended in paragraph (a)(9)(ii) and the second sentence of paragraphs (a)(9)(iii) and (a)(9)(iv) by adding after the word ''safety'' the phrase ''or efficacy'' each time it appears, and by revising paragraph (a)(9)(v) to read as follows:

§ 314.94 Content and format of an abbreviated application.

* * * * *

(a) * * *

(9) * * *

(v) *Inactive ingredient changes permitted in drug products intended for topical use.* Generally, a drug product intended for topical use, solutions for aerosolization or nebulization, and nasal solutions shall contain the same inactive ingredients as the reference listed drug identified by the applicant under paragraph (a)(3) of this section. However, an abbreviated application may include different inactive ingredients provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.

* * * * *

§ 314.127 [Amended]

3. Section 314.127 *Refusal to approve an abbreviated new drug application* is amended in the introductory text of paragraph (a)(8)(ii)(A), and in paragraphs (a)(8)(ii)(B) and (a)(8)(ii)(C) by adding after the word ''safety'' the phrase ''or efficacy'' each time it appears.

PART 320—BIOAVAILABILITY AND BIOEQUIVALENCE REQUIREMENTS

4. The authority citation for 21 CFR part 320 continues to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 355, 357, 371.

5. Section 320.1 is amended by revising paragraph (c) to read as follows:

§ 320.1 Definitions.

* * * * *

(c) *Pharmaceutical equivalents* means drug products in identical dosage forms that contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; do not necessarily contain the same inactive ingredients; and meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.

* * * * *

6. Section 320.21 is amended by removing paragraph (d)(1) and redesignating paragraphs (d)(2) and (d)(3) as paragraphs (d)(1) and (d)(2), respectively, and by revising newly redesignated (d)(2)(i) and (d)(2)(ii); and by revising paragraphs (a)(1), (a)(2), (b)(1), (b)(2), (c)(1), (e), and (f), the introductory text of paragraph (g), and paragraphs (g)(2) and (h) to read as follows:

§ 320.21 Requirements for submission of in vivo bioavailability and bioequivalence data.

(a) * * *

(1) Evidence measuring the in vivo bioavailability of the drug product that is the subject of the application; or

(2) Information to permit FDA to waive the submission of evidence measuring in vivo bioavailability.

(b) * * *

(1) Evidence demonstrating that the drug product that is the subject of the abbreviated new drug application is bioequivalent to the reference listed drug (defined in § 314.3(b) of this chapter); or

(2) Information to show that the drug product is bioequivalent to the reference listed drug which would permit FDA to waive the submission of evidence demonstrating in vivo bioequivalence as provided in paragraph (f) of this section.

(c) * * *

(1) A change in manufacturing site as well as a change in the manufacturing process, including a change in product formulation or dosage strength, beyond the variations provided for in the approved application.

* * * * *

(d) * * *

(2) * * *

(i) Evidence measuring the in vivo bioavailability and demonstrating the in vivo bioequivalence of the drug product that is the subject of the application; or

(ii) Information to permit FDA to waive measurement of in vivo bioavailability.

(e) Evidence measuring the in vivo bioavailability and demonstrating the in vivo bioequivalence of a drug product shall be obtained using one of the approaches for determining bioavailability set forth in § 320.24.

(f) Information to permit FDA to waive the submission of evidence measuring the in vivo bioavailability or demonstrating the in vivo bioequivalence shall meet the criteria set forth in § 320.22.

(g) Any person holding an approved full or abbreviated new drug application shall submit to FDA a supplemental application containing new evidence measuring the in vivo bioavailability or demonstrating the in vivo bioequivalence of the drug product that is the subject of the application if notified by FDA that:

* * * * *

(2) There are data measuring significant intra-batch and batch-to-batch variability, e.g., plus or minus 25 percent, in the bioavailability of the drug product.

(h) The requirements of this section regarding the submission of evidence measuring the in vivo bioavailability or demonstrating the in vivo bioequivalence apply only to a full or abbreviated new drug application or a supplemental application for a finished dosage formulation.

7. Section 320.22 is amended by revising paragraph (a), the second sentence of paragraph (b), paragraphs (b)(1)(ii), (b)(2)(ii), (b)(3)(i), (b)(3)(ii), (b)(3)(iii), and (c), the introductory text of paragraph (d), paragraphs (d)(2)(i) and (d)(4)(i), and the first sentence of paragraph (e) to read as follows:

§ 320.22 Criteria for waiver of evidence of in vivo bioavailability or bioequivalence.

(a) Any person submitting a full or abbreviated new drug application, or a supplemental application proposing any of the changes set forth in § 320.21(c), may request FDA to waive the requirement for the submission of evidence measuring the in vivo bioavailability or demonstrating the in vivo bioequivalence of the drug product that is the subject of the application. An applicant shall submit a request for waiver with the application. Except as provided in paragraph (f) of this section, FDA shall waive the requirement for the submission of evidence of in vivo bioavailability or bioequivalence if the drug product meets any of the provisions of paragraphs (b), (c), (d), or (e) of this section.

(b) * * * FDA shall waive the requirement for the submission of evidence obtained in vivo measuring the bioavailability or demonstrating the bioequivalence of these drug products.

* * *

(1) * * *

(ii) Contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application or abbreviated new drug application.

(2) * * *

(ii) Contains an active ingredient in the same dosage form as a drug product that is the subject of an approved full new drug application or abbreviated new drug application.

(3) * * *

(i) Is a solution for application to the skin, an oral solution, elixir, syrup, tincture, a solution for aerosolization or nebulization, a nasal solution, or similar other solubilized form.

(ii) Contains an active drug ingredient in the same concentration and dosage form as a drug product that is the subject of an approved full new drug application or abbreviated new drug application; and

(iii) Contains no inactive ingredient or other change in formulation from the drug product that is the subject of the approved full new drug application or abbreviated new drug application that may significantly affect absorption of the active drug ingredient or active moiety.

(c) FDA shall waive the requirement for the submission of evidence measuring the in vivo bioavailability or demonstrating the in vivo bioequivalence of a solid oral dosage form (other than a delayed release or extended release dosage form) of a drug product determined to be effective for at least one indication in a Drug Efficacy Study Implementation notice or which is identical, related, or similar to such a drug product under § 310.6 of this chapter unless FDA has evaluated the drug product under the criteria set forth in § 320.33, included the drug product in the Approved Drug Products with Therapeutic Equivalence Evaluations List, and rated the drug product as

having a known or potential bioequivalence problem. A drug product so rated reflects a determination by FDA that an in vivo bioequivalence study is required.

(d) For certain drug products, bioavailability may be measured or bioequivalence may be demonstrated by evidence obtained in vitro in lieu of in vivo data. FDA shall waive the requirement for the submission of evidence obtained in vivo measuring the bioavailability or demonstrating the bioequivalence of the drug product if the drug product meets one of the following criteria:

* * * * *

(2) * * *

(i) The bioavailability of this other drug product has been measured;

* * * * *

(4) * * *

(i) The bioavailability of the other product has been measured; and

* * * * *

(e) FDA, for good cause, may waive a requirement for the submission of evidence of in vivo bioavailability or bioequivalence if waiver is compatible with the protection of the public health.

* * *

* * * * *

8. Section 320.23 is amended by revising the section heading and the first sentence of paragraph (a)(1) to read as follows:

§ 320.23 Basis for measuring in vivo bioavailability or demonstrating bioequivalence.

(a)(1) The in vivo bioavailability of a drug product is measured if the product's rate and extent of absorption, as determined by comparison of measured parameters, e.g., concentration of the active drug ingredient in the blood, urinary excretion rates, or pharmacological effects, do not indicate a significant difference from the reference material's rate and extent of absorption. * * *

* * * * *

9. Section 320.24 is amended by revising the section heading and the first, second, and last sentences of paragraph (a), by removing paragraph (b)(1)(iii), by revising the first, second, and last sentences of paragraph (b)(4), paragraphs (b)(5) and (b)(6), and the introductory text of paragraph (c) to read as follows:

§ 320.24 Types of evidence to measure bioavailability or establish bioequivalence.

(a) Bioavailability may be measured or bioequivalence may be demonstrated by several in vivo and in vitro methods. FDA may require in vivo or in vitro testing, or both, to measure the bioavailability of a drug product or establish the bioequivalence of specific drug products. * * * The method used must be capable of measuring bioavailability or establishing bioequivalence, as appropriate, for the product being tested.

(b) * * *

(4) Well-controlled clinical trials that establish the safety and effectiveness of the drug product, for purposes of measuring bioavailability, or appropriately designed comparative clinical trials, for purposes of demonstrating bioequivalence. This approach is the least accurate, sensitive, and reproducible of the general approaches for measuring bioavailability or demonstrating bioequivalence. * * * This approach may also be considered sufficiently accurate for measuring bioavailability or demonstrating bioequivalence of dosage forms intended to deliver the active moiety locally, e.g., topical preparations for the skin, eye, and mucous membranes; oral dosage forms not intended to be absorbed, e.g., an antacid or radiopaque medium; and bronchodilators administered by inhalation if the onset and duration of pharmacological activity are defined.

(5) A currently available in vitro test acceptable to FDA (usually a dissolution rate test) that ensures human in vivo bioavailability.

(6) Any other approach deemed adequate by FDA to measure bioavailability or establish bioequivalence.

(c) FDA may, notwithstanding prior requirements for measuring bioavailability or establishing bioequivalence, require in vivo testing in humans of a product at any time if the agency has evidence that the product:

* * * * *

10. Section 320.25 is amended by removing paragraph (a)(2), by redesignating paragraph (a)(3) as paragraph (a)(2), and by revising paragraph (d)(1), the introductory text of paragraph (e)(1), and paragraph (e)(1)(i) to read as follows:

§ 320.25 Guidelines for the conduct of an in vivo bioavailability study.

* * * * *

(d) *Previously unmarketed active drug ingredients or therapeutic moieties.* (1) An in vivo bioavailability study involving a drug product containing an active drug ingredient or therapeutic moiety that has not been approved for marketing can be used to measure the following pharmacokinetic data:

* * * * *

(e) *New formulations of active drug ingredients or therapeutic moieties approved for marketing.* (1) An in vivo bioavailability study involving a drug product that is a new dosage form, or a new salt or ester of an active drug ingredient or therapeutic moiety that has been approved for marketing can be used to:

(i) Measure the bioavailability of the new formulation, new dosage form, or new salt or ester relative to an appropriate reference material; and

* * * * *

11. Section 320.26 is amended by revising the section heading and paragraphs (a)(1) and (b)(2)(i) to read as follows:

§ 320.26 Guidelines on the design of a single-dose in vivo bioavailability or bioequivalence study.

(a) *Basic principles.* (1) An in vivo bioavailability or bioequivalence study should be a single-dose comparison of the drug product to be tested and the appropriate reference material conducted in normal adults.

* * * * *

(b) * * *

(2) * * *

(i) At least five times the half-life of the active drug ingredient or therapeutic moiety, or its active metabolite(s), measured in the blood or urine; or

* * * * *

12. Section 320.27 is amended by revising the section heading, introductory text of paragraph (a)(3), paragraphs (d)(1), (d)(2), and (e)(3); and by adding in paragraph (b)(3)(i) the word ''active'' before the word ''metabolite(s),'' to read as follows:

§ 320.27 Guidelines on the design of a multiple-dose in vivo bioavailability or bioequivalence study.

(a) * * *

(3) A multiple-dose study may be required to determine the bioavailability or bioequivalence of a drug product in the following circumstances:

* * * * *

(d) *Collection of blood or urine samples.* (1) Whenever comparison of the test product and the reference material is to be based on blood concentration-time curves at steady-state, sufficient samples of blood should be taken to define adequately the predose blood concentration on 3 or more consecutive days to establish that steady-state conditions are achieved.

(2) Whenever comparison of the test product and the reference material is to be based on cumulative urinary excretion-time curves at steady-state, sufficient samples of urine should be taken to define the rate and extent of

urinary excretion on 3 or more consecutive days to establish that steady-state conditions are achieved.

* * * * *

(e) * * *

(3) Other methods based on valid scientific reasons should be used to determine the bioavailability or bioequivalence of a drug product having dose-dependent kinetics (nonlinear system).

* * * * *

13. Section 320.29 is amended by revising the section heading and paragraph (a) to read as follows:

§ 320.29 Analytical methods for an vivo bioavailability or bioequivalence study.

(a) The analytical method used in an in vivo bioavailability or bioequivalence study to measure the concentration of the active drug ingredient or therapeutic moiety, or its metabolite(s), in body fluids or excretory products, or the method used to measure an acute pharmacological effect shall be demonstrated to be accurate and of sufficient sensitivity to measure, with appropriate precision, the actual concentration of the active drug ingredient or therapeutic moiety, or its metabolite(s), achieved in the body.

* * * * *

14. Section 320.30 is amended by revising paragraph (c) to read as follows:

§ 320.30 Inquiries regarding bioavailability and bioequivalence requirements and review of protocols by the Food and Drug Administration.

* * * * *

(c)(1) General inquiries relating to in vivo bioavailability requirements and methodology shall be submitted to the Food and Drug Administration, Center for Drug Evaluation and Research, Office of Clinical Pharmacology and Biopharmaceutics (HFD–850), 5600 Fishers Lane, Rockville, MD 20857.

(2) General inquiries relating to bioequivalence requirements and methodology shall be submitted to the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Bioequivalence (HFD–650), 7500 Standish Pl., Rockville, MD 20855–2773.

§ 320.31 [Amended]

15. Section 320.31 *Applicability of requirements regarding an ''Investigational New Drug Application* is amended in the introductory text of paragraph (b) by adding after the word ''bioavailability'' the phrase ''or bioequivalence''.

Dated: November 5, 1998.

William B. Schultz,

Deputy Commissioner for Policy.

[FR Doc. 98–30880 Filed 11–18–98; 8:45 am]

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ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 52

[WA 67–7142b; FRL–6188–2]

Approval and Promulgation of State Implementation Plans: Washington

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed rule.

SUMMARY: The EPA proposes to approve the State Implementation Plan (SIP) revision submitted by the State of Washington for the purpose of including a variance to a permit issued to the U.S. Army for the operation of three heat recovery incinerators located at Fort Lewis by local air pollution control agency, the Puget Sound Air Pollution Contol Agency (PSAPCA). In the Final Rules Section of this **Federal Register**, the EPA is approving the State's SIP submittal as a direct final rule without prior proposal because the Agency views this as a noncontroversial submittal amendment and anticipates no adverse comments. A detailed rationale for the approval is set forth in the direct final rule. If no adverse comments are received in response to this action, no further activity is contemplated. If the EPA receives adverse comments, the direct final rule will be withdrawn and all public comments received will be addressed in a subsequent final rule based on this proposed rule. The EPA will not institute a second comment period. Any parties interested in commenting on this action should do so at this time.

DATES: Written comments must be received in writing by December 21, 1998.

ADDRESSES: Written comments should be addressed to Montel Livingston, Environmental Protection Specialist (OAQ–107), Office of Air Quality, at the EPA Regional Office listed below. Copies of the documents relevant to this proposed rule are available for public inspection during normal business hours at the following locations. The interested persons wanting to examine these documents should make an appointment with the appropriate office at least 24 hours before the visiting day.

Environmental Protection Agency, Region 10, Office of Air Quality, 1200 6th Avenue, Seattle, WA 98101

The Washington State Department of Ecology, Air Quality Program, 300 Desmond Drive, Lacey, WA 98503

FOR FURTHER INFORMATION CONTACT: Mahbubul Islam, Office of Air Quality (OAQ–107), EPA, 1200 6th Avenue, Seattle, WA 98101, (206) 553–6985.

SUPPLEMENTARY INFORMATION:

See the information provided in the Direct Final action which is located in the Rules Section of this **Federal Register**.

Dated: November 3, 1998.

Jane S. Moore,

Acting Regional Administrator, Region 10.

[FR Doc. 98–30848 Filed 11–18–98; 8:45 am]

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DEPARTMENT OF COMMERCE

National Oceanic and Atmospheric Administration

50 CFR Part 216

[I.D. 110998A]

Regulations Governing the Taking and Importing of Marine Mammals; Threatened Fish and Wildlife; Cook Inlet Beluga Whales

AGENCY: National Marine Fisheries Service (NMFS), National Oceanic and Atmospheric Administration (NOAA), Commerce.

ACTION: Notice of intent to conduct a status review and request for information.

SUMMARY: NMFS is initiating a status review of the Cook Inlet beluga whale (*Delphinapterus leucas*) to determine whether designation under the Marine Mammal Protection Act (MMPA) or a change in listing classification under the Endangered Species Act (ESA) is warranted. NMFS intends to undertake the review in conjunction with the Alaska Beluga Whale Committee and the Cook Inlet Marine Mammal Council. The review will give consideration to the current status of Cook Inlet belugas, their distribution, abundance and trends, food habits, biohealth parameters, and reproductive parameters. The effects of the Native subsistence harvest, and the potential effects of other humanly induced impacts, as well as beluga natural mortality will also be examined. To ensure that the review is comprehensive, NMFS is requesting that interested parties submit pertinent information and comments regarding