(ii) One or more construction contracts (includes any contract awarded by the recipient) subject to such requirements or prohibitions had been awarded.

(4) The Assistant Administrator for Procurement may exempt a particular project, contract, or subcontract from this policy upon a finding that special circumstances require an exemption in order to avert an imminent threat to public health or safety, or to serve the national security. A finding of ''special circumstances'' may not be based on the possibility or presence of a labor dispute concerning the use of contractors or subcontractors who are nonsignatories to, or otherwise do not adhere to, agreements with one or more labor organizations, or concerning employees on the project who are not members of, or affiliated with, a labor organization.

PART 1274—COOPERATIVE AGREEMENTS WITH COMMERCIAL FIRMS

3. The authority citation for part 1274 continues to read as follows:

Authority: 31 U.S.C. 6301 to 6308; 42 U.S.C. 2451 *et seq.*

4. 1274.215 is added to read as follows:

§ 1274.215 Federal and federally funded construction projects.

(a) In accordance with E.O. 13202 of February 17, 2001, ''Preservation of Open Competition and Government Neutrality Towards Government Contractors' Labor Relations on Federal and Federally Funded Construction Projects'', as amended on April 6, 2001, the Government, or any construction manager acting on behalf of the Government, shall not—

(1) Require or prohibit recipients, potential recipients or subrecipients to enter into or adhere to agreements with one or more labor organizations (as defined in 42 U.S.C. 2000e(d)) on the same or other related construction projects; or

(2) Otherwise discriminate against recipients, potential recipients or subrecipients for becoming, refusing to become, or remaining signatories or otherwise adhering to agreements with one or more organizations, on the same or other related construction projects.

(b) Nothing in this section prohibits the recipient, potential recipients or subrecipients from voluntarily entering into project labor agreements.

(c) The Assistant Administrator for Procurement may exempt a construction project from this policy if, as of February 17, 2001—

(1) The agency or a construction manager acting on behalf of the Government had issued or was party to bid specifications, project agreements, agreements with one or more labor organizations, or other controlling documents with respect to that particular project, which contained any of the requirements or prohibitions in paragraph (d)(1) of this section; and

(2) One or more construction contracts (includes any contract awarded by the recipient) subject to such requirements or prohibitions had been awarded.

(d) The Assistant Administrator for Procurement may exempt a particular project, contract, or subcontract from this policy upon a finding that special circumstances require an exemption in order to avert an imminent threat to public health or safety, or to serve the national security. A finding of ''special circumstances'' may not be based on the possibility or presence of a labor dispute concerning the use of contractors or subcontractors who are nonsignatories to, or otherwise do not adhere to, agreements with one or more labor organizations, or concerning employees on the project who are not members of, or affiliated with, a labor organization.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 314 and 320

[Docket No. 98N–0778]

RIN 0910–AC47

Bioavailability and Bioequivalence Requirements; Abbreviated Applications; Final Rule

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending 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: This rule is effective February 18, 2003.

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) to provide information pertaining to bioavailability and bioequivalence (§ 314.94(a)(7) (21 CFR 314.94(a)(7)).

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 (Public Law 98–417).

In the **Federal Register** of November 19, 1998 (63 FR 64222), FDA proposed to revise its regulations on bioavailability and bioequivalence and the content and format of an ANDA to reflect current FDA policy and to correct certain typographical and inadvertent errors (the proposed rule). The publication of this final rule completes this rulemaking.

II. Description of the Final Rule

FDA is finalizing the proposed rule with the following revisions made in response to comments received on the proposal.

As proposed, the final rule changes the term ''enteric coated'' to ''delayed release'' and the term ''controlled release'' to ''extended release'' in § 320.22(c). To conform to this change, the final rule also amends §§ 320.1, 320.22(d)(2)(iv), 320.25(f), 320.27(a)(3)(iv), 320.27(b)(2), 320.28, and 320.31 by changing ''controlled release'' to ''extended release.'' To conform to the new terminology, the final rule also amends § 320.25(f) by changing ''noncontrolled release'' to ''nonextended release.''

The following new first sentence has been added to redesignated § 320.25(a)(2): ''An in vivo bioavailability study is generally done in a normal adult population under standardized conditions.'' This sentence is a necessary lead-in for the existing text that refers to situations in which

bioavailability studies may be conducted in patients.

The proposed rule would have revised § 320.26(b)(2)(i) to require a customary drug elimination period of five times, rather than at least three times, the half-life of the active drug ingredient or therapeutic moiety, or its active metabolite(s). In response to a comment pointing out that a drug elimination period of five half-lives may be impractically long for a drug with a long half-life, the agency has decided not to revise § 320.26(b)(2)(i).

The proposed rule would have revised § 320.27(d)(1) and (d)(2) to state that blood or urine samples should be taken on 3 or more consecutive days to establish that steady-state conditions have been achieved. Some comments stated that obtaining samples on consecutive days may be impractical and, for drugs with long half-lives, may be less sensitive to the establishment of steady state than data obtained over a longer period of time. The final rule requires that ''appropriate dosage administration and sampling should be carried out to document steady state.'' Specific advice about dosage administration and sampling may be obtained from the appropriate review division for the drug product.

III. Comments on the Proposed Rule

The agency received seven comments from pharmaceutical companies, pharmaceutical company trade associations, and a law firm.

A. Inactive Ingredients

Section 314.94(a)(9) establishes information requirements for the chemistry, manufacturing, and controls section of an abbreviated application. Section 314.94(a)(9)(ii) through (v) 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 agency proposed to amend this section to recognize the possibility that the use of different inactive ingredients can also affect a product's efficacy.

(Comment 1) We received several comments about the addition of the word ''efficacy.'' One comment said this change is unnecessary because demonstrating bioequivalence provides proof of efficacy. One comment interpreted the change as suggesting that FDA is departing from its position that bioequivalence shows that the generic product is as effective as its reference listed drug. This comment asked what additional proof of effectiveness FDA would require. One comment agreed with the proposed change and asked that it apply to pending ANDA's. This comment also stated that animal tests should not be used to demonstrate that different inactive ingredients do not affect safety or efficacy because the act prohibits the use of animal or clinical studies to establish that the drug is safe or effective. Another comment expressed concern that the need to show that a different inactive ingredient does not affect safety or efficacy makes it more difficult to get approval for a generic topical drug product because clinical trials must be conducted.

As stated in the proposed rule, by adding the word ''efficacy,'' the agency acknowledges the possibility that the use of different inactive ingredients can also affect a product's efficacy. FDA is not departing from its position that a generic product that demonstrates bioequivalence to the reference listed drug has shown that it is as effective as that reference listed drug.

The agency disagrees with the comment stating the animal tests should not be used in the process of assessing the safety or efficacy of inactive ingredients that differ from those in the reference listed drug. In the preamble to the proposed ANDA regulations, the agency suggested that data from animal studies might be used as limited confirmatory testing to support an ANDA suitability petition or an ANDA resulting from such a petition (54 FR 28872 at 28880, July 10, 1989). The preamble cited as an example the use of limited confirmatory testing to show that an approved change in an active ingredient did not have acute effects on the safety of the product. In similar fashion, animal studies may be useful and appropriate to assist FDA in evaluating the safety or the effect on efficacy of a changed inactive ingredient.

Section 314.127 (21 CFR 314.127) lists the reasons why FDA will refuse to approve an ANDA. The agency proposed to 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.

(Comment 2) One comment stated that the proposed change is consistent with FDA's current policy when applied to parenteral and ophthalmic dosage forms, but otherwise is inconsistent with current policy. Another comment said this change is unnecessary because demonstrating bioequivalence provides proof of efficacy.

As stated in the proposed rule, and in the response to the previous comment, the addition of the word ''efficacy'' simply clarifies the current FDA approach rather than effecting a substantive change.

B. Pharmaceutical Equivalents

Proposed § 320.1(c) revised the definition of ''pharmaceutical equivalents'' with regard to drug products that contain a reservoir that facilitates delivery or where residual volume may vary.

(Comment 3) One comment approved of the change. The final rule is unchanged from the proposed rule.

C. Manufacturing Site Change

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 agency proposed to 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.

(Comment 4) Several comments asserted that this proposed change is inconsistent with FDA's guidance ''Immediate Release Solid Oral Dosage Forms—Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation'' (November 1995) (SUPAC–IR guidance), which does not specify a demonstration of bioequivalence for level 1–3 changes. The comments recommended that any change to the regulation be consistent with the SUPAC–IR guidance.

FDA believes that this change is consistent with the SUPAC–IR guidance. The SUPAC–IR guidance describes the levels of changes, recommended tests, and filing documentation that ensure continuing product quality and performance characteristics of an immediate release dosage form for specific postapproval changes. Depending on the level of change and the solubility and permeability characteristics of the active drug substance, the SUPAC–IR guidance recommends different levels of in vitro dissolution tests and/or in vivo bioequivalence studies. The addition of a change in the manufacturing site to

§ 320.21(c)(1) does not mean that the agency would require an in vivo demonstration of bioequivalence in the circumstances provided for in the SUPAC–IR guidance. For manufacturing site changes, dissolution testing alone is generally sufficient to ensure unchanged product quality and performance for an immediate release solid oral dosage form. FDA expects to continue to follow the SUPAC–IR guidance in implementing § 320.21(c)(1) as revised.

D. Delayed Release and Extended Release Terminology

The agency proposed to amend § 320.22(c) to change ''enteric coated'' to ''delayed release'' and ''controlled release'' to ''extended release.''

(Comment 5) One comment stated that these terms should also be replaced in § 320.22(d)(2)(iv).

FDA agrees with this comment. The final rule amends § 320.22(d)(2)(iv) by changing ''enteric coated'' to ''delayed release'' and ''controlled release'' to ''extended release.'' The final rule also amends §§ 320.1, 320.25(f), 320.27(a)(3)(iv), 320.27(b)(2), 320.28, and 320.31 by changing ''controlled release'' to ''extended release.'' To conform to these changes, the final rule also amends § 320.25(f) by changing ''noncontrolled release'' to ''nonextended release.''

E. Bioavailability Is Measured

Section 320.24 describes the types of evidence needed to establish bioavailability or bioequivalence. Instead of stating that bioavailability is demonstrated or established, the agency proposed to use the word ''measured.''

(Comment 6) One comment objected to this across-the-board change, asserting that it is not possible to get a quantitative measure of bioavailability from an acute pharmacological effect, a well-controlled clinical trial, or an in vitro test. The comment suggested that the words ''demonstrated'' or ''established'' be used in discussing these types of evidence.

FDA disagrees with this comment. Bioavailability is an observational measure that always results in a quantitative figure. Therefore, the final rule will remain as it was proposed.

F. Subjects for Bioavailability Studies

The agency proposed to remove § 320.25(a)(2) and redesignate § 320.25(a)(3) as § 320.25(a)(2). Current § 320.25(a)(2) provides in part 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.''

(Comment 7) One comment proposed the following new first sentence for redesignated § 320.25(a)(2): ''An in vivo bioavailability study shall ordinarily be done in normal adults under standardized conditions.'' The comment stated that this sentence is a necessary lead-in for the existing text that refers to situations in which bioavailability studies may be conducted in patients.

FDA agrees with this comment and has included similar language in the final rule.

G. Drug Elimination Period

Proposed § 320.26(b)(2)(i) stated that the customary drug elimination period should be five times the half-life of the active drug ingredient or therapeutic moiety, or its active metabolite(s).

(Comment 8) FDA received several comments on this section. One comment approved of the change from the three half-lives in the current regulation, while another comment recommended four half-lives. One comment disagreed with using half-life multiples to establish the duration of sampling because the terminal half-life is a function of the study design and the sensitivity of the assay and, in many cases, represents the elimination of small amounts of drug from deep compartments. In those cases, a five half-life requirement may greatly overestimate the time needed to measure the area under the curve (AUC) extrapolated to infinity. The comment recommended that the rule state: ''The duration of blood sampling should be adequate to insure that the measured AUC represents at least 90% of AUC (infinity)'' (AUC_∞). Another comment, noting that many drugs exhibit multiexponential serum concentration-time profiles, asked FDA to substitute ''97% of the AUC_∞'' for ''five times the half-life.''

The agency recognizes that for a drug with a long half-life, a drug elimination period of five half-lives may be impractically long. FDA has concluded that a drug elimination period of three half-lives, which characterizes approximately 88 percent of the AUC_∞, is sufficent. Therefore, the final rule leaves § 320.26(b)(2)(i) unchanged.

(Comment 9) One comment suggested that § 320.26(b)(2) should use an alternative phrase such as ''washout period'' or ''time between dosings'' rather than the term ''drug elimination period'' because that term could be confused with the concept of drug elimination. FDA disagrees with this comment. The term ''drug elimination period'' has been used in § 320.26(b)(2) since the bioequivalence regulations were finalized in 1992, and the agency has not found that it causes confusion. Drug elimination is the metabolic process that eliminates the drug from the body. The drug elimination period is the time allowed for subjects to clear the first drug from the body before giving the second drug. The term ''drug elimination period'' is retained in the final rule.

H. Sampling to Establish Steady State

Proposed § 320.27(d)(1) and (d)(2) would have required sampling on 3 or more consecutive days to establish that steady-state conditions have been achieved whenever comparison of the test product and the reference material is to be based on blood concentration-time curves at steady state or urinary excretion-time curves at steady state.

(Comment 10) Several comments suggested deleting the word ''consecutive'' from § 320.27(d)(1). One comment stated that drugs with long half-lives accumulate slowly and the use of data from consecutive days for such drugs is less sensitive to the establishment of steady state than data obtained over a longer period of time. Another comment said that the 3–consecutive-day requirement is often not practical, particularly for urinary collection, and proposed dosing drugs for five to six half-lives or 1 week, whichever is longer, and then sampling blood or urine over one dosing interval.

One comment agreed that it is appropriate to obtain samples on 3 or more consecutive days. This comment stated that sometimes predose blood concentrations may be below the limit of quantitation; then it would not be possible to confirm attainment of steady state. The comment recommended that the predose collection time should be at a time when the blood drug concentrations are in the reliable range of quantitation of the assay and will be identical on all 3 days for all subjects.

Another comment stated that the proposed change to § 320.27(d)(1) reflects current practice, but that the requirement for consecutive-day data in § 320.27(d)(2) is unnecessarily restrictive. This comment proposed eliminating the word ''consecutive'' and instead saying ''to define adequately the predose blood concentration on 3 or more days (or doses) to establish that steady-state conditions are achieved.''

The agency has carefully considered these comments and has decided not to require that sampling be done on 3 or more consecutive days. Therefore, FDA has revised § 320.27(d)(1) and (d)(2) to state that ''* * * appropriate dosage administration and sampling should be carried out to document attainment of steady state.''

Current § 320.27(d)(1) requires that blood sampling be sufficient to define both the minimum (Cmin) and maximum (Cmax) blood concentrations on 2 or more consecutive days to establish that steady-state conditions have been achieved. The preamble to the proposed rule explained that one of the reasons the agency proposed to revise § 320.27(d)(1) is that FDA no longer uses Cmax values to determine steady-state conditions. The proposed rule also stated that, in some cases, the predose trough level may not be the observed Cmin value.

(Comment 11) One comment stated that the agency's proposal to revise § 320.27(d)(1) appeared contradictory because it would require that trough samples be measurable in order to establish steady state. The comment stated: ''The Agency should address these drugs (or drug products) which have a relatively short half-life (relative to the pharmacodynamic effect and dosing interval). Is it still acceptable to measure only trough values when the concentrations are less than the analytical lower limit of quantitation?''

As discussed in the response to comment 10, the agency is not revising § 320.27(d)(1) as set forth in the proposed rule. Instead, the final rule revises § 320.27(d)(1) to state that ''* * * appropriate dosage administration and sampling should be carried out to document attainment of steady state.'' This revision will permit the sampling schedule used to document steady state to be tailored to the characteristics of the drug being studied. Specific questions about the appropriateness and design of multiple-dose studies should be directed to the appropriate review division in the Office of New Drugs or to the Office of Generic Drugs.

I. Addition of Bioequivalence

The proposed rule added the words ''or bioequivalence'' after the word ''bioavailability'' in the section heading of § 320.27 and throughout the section.

(Comment 12) One comment pointed out that the preamble to the proposed rule did not discuss the addition of the words ''or bioequivalence'' to § 320.27(e)(3). The comment has caused the agency to reconsider its proposal to amend § 320.27 to apply to bioequivalence as well as bioavailability. Section 320.27 discusses circumstances in which multiple-dose studies may be needed. FDA's current scientific thinking is that single-dose pharmacokinetic studies are preferable to multiple-dose studies to demonstrate bioequivalence because they are generally more sensitive in assessing release of the drug substance from the drug product into the systemic circulation. Accordingly, the agency has decided not to add the words ''or bioequivalence'' to § 320.27.

J. Additional Definitions

Proposed § 320.29(a) added the words ''or bioequivalence'' after the word ''bioavailability'' to the discussion of the analytical method used in an in vivo study.

(Comment 13) One comment asked FDA to revise § 320.29(a) to include several definitions. The comment suggested that ''active'' metabolite should be defined because the concept is vague and many metabolites that are present in low concentrations may not contribute to the overall activity of the drug. In addition, the comment stated that FDA should define active metabolites with respect to their activity relative to the parent drug and relative concentration. This comment also asked FDA to define the ''sufficient sensitivity'' that is required to measure the active drug and/or metabolites. The comment said that it is reasonable to expect laboratories to provide a calibration range that provides a 32-fold range (5 half-lives) from the mean Cmax to the lower limit of quantitation, and this range is more than adequate to define more than 95 percent of the plasma AUC.

FDA declines to add definitions of these concepts to § 320.29(a). Ascertaining the active metabolite can be a complex matter that requires a case-by-case approach rather than a regulatory definition. In October 2000, the agency published a guidance entitled ''Bioavailability and Bioequivalence Studies for Orally Administered Drug Products—General Considerations'' that discusses moieties that should be measured in bioavailability and bioequivalence studies.

K. Miscellaneous Changes

The final rule replaces the period at the end of § 320.22(b)(3)(i) with a semicolon and the word ''and''.

The proposed rule added to § 320.22(b)(3)(i) the language ''a solution for aerosolization or nebulization, a nasal solution.'' To conform to this change, the final rule adds language to § 320.22(b)(3)(iii) to indicate that products intended to act locally such as a solution for aerosolization or nebulization or a nasal solution should not contain an 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 systemic or local availability.

The proposed rule added the word ''active'' before the word ''metabolite(s)'' in § 320.27(b)(3)(i). To conform to this addition, the final rule amends § 320.29 to add the word ''active'' before the word ''metabolite(s).''

IV. Environmental Impact

The agency has determined under 21 CFR 25.30(h) through (k) 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.

V. Analysis of Impacts

FDA has examined the impacts of the final rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this final rule is consistent with the regulatory philosophy and principles identified in the Executive order. The final rule amends the bioavailability and bioequivalence regulations to reflect current FDA policy. Thus, the final rule is not a significant action as defined by the Executive order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options to minimize any significant impact on a substantial number of small entities. The agency certifies that the final rule would not have a significant impact on a substantial number of small entities because the final rule merely amends the bioavailability and bioequivalence regulations to reflect current FDA practice. Therefore, under the Regulatory Flexibility Act, no further analysis is required.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 (Public Law 104–4) requires that agencies prepare a written statement of anticipated costs and benefits before proposing any rule that may result in an expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100 million or more in any one year (adjusted annually for inflation). The Unfunded Mandates Reform Act does not require FDA to prepare a statement of costs and benefits for the final rule because the rule is not

expected to result in any 1-year expenditure that would exceed $100 million adjusted for inflation. The current inflation-adjusted statutory threshold is $110 million.

VI. Paperwork Reduction Act of 1995

FDA concludes that this final rule does not require information collections subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (Public Law 104–13).

VII. Executive Order 13132: Federalism

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

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, 21 CFR parts 314 and 320 are amended as follows:

PART 314—APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW 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, 355a, 356, 356a, 356b, 356c, 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 the phrase ''or efficacy'' after the word ''safety'' 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 paragraph (a)(8)(ii)(A) introductory text and in paragraphs (a)(8)(ii)(B) and (a)(8)(ii)(C) by adding the phrase ''or efficacy'' after the word ''safety'' 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, 371.

5. Section 320.1 is amended in paragraph (e) by removing the word ''controlled'' and adding in its place the word ''extended'' and 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:

a. Removing paragraph (d)(1);

b. Redesignating paragraphs (d)(2) and (d)(3) as paragraphs (d)(1) and (d)(2), respectively;

c. Revising newly redesignated paragraphs (d)(2)(i) and (d)(2)(ii); and

d. Revising paragraphs (a)(1), (a)(2), (b)(1), (b)(2), (c)(1), (e), and (f), paragraph (g) introductory text, and paragraphs (g)(2) and (h).

The revisions 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 the manufacturing site or 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) introductory text, paragraphs (b)(1)(ii), (b)(2)(ii), (b)(3)(i), (b)(3)(ii), (b)(3)(iii), and (c), paragraph (d) introductory text, paragraphs (d)(2)(i), (d)(2)(iv), 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; and

(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 for products that are systemically absorbed, or that may significantly affect systemic or local availability for products intended to act locally.

(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;

* * * * *

(iv) Paragraph (d) of this section does not apply to delayed release or extended release products.

* * * * *

(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:

a. Revising the section heading and the first, second, and last sentences of paragraph (a);

b. Removing paragraph (b)(1)(iii); and

c. Revising the first, second, and last sentences of paragraph (b)(4), paragraphs (b)(5) and (b)(6), and paragraph (c) introductory text.

The revisions 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:

a. Removing paragraph (a)(2);

b. Redesignating paragraph (a)(3) as paragraph (a)(2);

c. Revising newly redesignated paragraph (a)(2), paragraph (d)(1), paragraph (e)(1) introductory text, and paragraph (e)(1)(i);

d. Revising the heading of paragraph (f) to read ''Extended release formulations.'';

e. Removing from paragraph (f) the word ''controlled'' each time it appears and adding in its place the word ''extended''; and

f. Removing from paragraph (f)(iii) the word ''noncontrolled'' and adding in its place the word ''nonextended''.

The revisions read as follows:

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

(a) * * *

(2) An in vivo bioavailability study is generally done in a normal adult population under standardized conditions. In some situations, an in vivo bioavailability study in humans may preferably and more properly be done in suitable patients. Critically ill patients shall not be included in an in vivo bioavailability study unless the attending physician determines that there is a potential benefit to the patient.

* * * * *

(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 paragraph (a)(1) 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.

* * * * *

12. Section 320.27 is amended by:

a. Revising paragraphs (a)(3)(iv), (d)(1), and (d)(2);

b. Removing from paragraph (b)(2) the word ''controlled'' and adding in its place the word ''extended''; and

c. Adding in paragraph (b)(3)(i) the word ''active'' before the word ''metabolite(s),''.

The additions and revisions read as follows:

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

(a) * * *

(3) * * *

(iv) The drug product is an extended release dosage form.

* * * * *

(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, appropriate dosage administration and sampling should be carried out to document attainment of steady state.

(2) Whenever comparison of the test product and the reference material is to be based on cumulative urinary excretion-time curves at steady state, appropriate dosage administration and sampling should be carried out to document attainment of steady state.

* * * * *

§ 320.28 [Amended]

13. Section 320.28 *Correlation of bioavailability with an acute pharmacological effect or clinical evidence* is amended by removing the word ''controlled'' and adding in its place the word ''extended''.

14. Section 320.29 is amended by revising the section heading and paragraph (a) and by adding the word ''active'' before the word ''metabolite(s)'' in paragraph (b) to read as follows:

§ 320.29 Analytical methods for an in 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 active 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 active metabolite(s), achieved in the body.

* * * * *

15. 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]

16. Section 320.31 *Applicability of requirements regarding an ''Investigational New Drug Application''* is amended in paragraph (b) introductory text by adding after the word ''bioavailability'' the phrase ''or bioequivalence'' and in paragraph (b)(3) by removing the word ''controlled'' and adding in its place the word ''extended''.

Dated: December 8, 2002.

Margaret M. Dotzel,

Assistant Commissioner for Policy.

[FR Doc. 02–31996 Filed 12–18–02; 8:45 am]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 878

[Docket No. 99P–5589]

Medical Devices; Reclassification and Codification of the Absorbable Polydioxanone Surgical Suture

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is announcing that it has issued an order in the form of a letter to Ethicon, Inc., reclassifying the absorbable polydioxanone surgical (PDS) suture intended for use in soft tissue approximation, including use in pediatric cardiovascular tissue where growth is expected to occur and ophthalmic surgery, from class III (premarket approval) to class II (special controls). Elsewhere in this issue of the **Federal Register**, FDA is announcing the availability of the guidance document entitled ''Class II Special Controls Guidance Document: Surgical Sutures; Guidance for Industry and FDA,'' which is immediately in effect as the special control for the PDS suture, but remains subject to public comment and possible future revision under the agency's good guidance practices. The agency is reclassifying this device into class II because new information supplied by the petitioner indicates that special controls, in addition to general controls, will provide reasonable assurance of the safety and effectiveness of the device, and there is sufficient information to establish special controls. Accordingly, the order is being codified in the Code of Federal Regulations. Any firm submitting a premarket notification (510(k)) for a new PDS suture will need to address the issues covered in the special control guidance. However, the firm need only show that its device meets the recommendations of the guidance or in some other way provides equivalent assurances of safety and effectiveness.

DATES: This rule is effective January 21, 2003. The reclassification was effective September 4, 2001.

FOR FURTHER INFORMATION CONTACT: Anthony D. Watson, Center for Devices and Radiological Health (HFZ–410), Food and Drug Administration, 9200 Corporate Blvd., Rockville, MD 20850, 301–594–3090.

SUPPLEMENTARY INFORMATION:

I. Background

The Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 301 *et seq.*), as amended by the Medical Device Amendments of 1976 (the 1976 amendments) (Public Law 94–295), the Safe Medical Devices Act of 1990 (the SMDA) (Public Law 101–629), and the Food and Drug Administration Modernization Act of 1997 (FDAMA) (Public Law 105–115), established a comprehensive system for the regulation of medical devices intended for human use. Section 513 of the act (21 U.S.C. 360c) establishes three categories (classes) of devices, depending on the regulatory controls needed to provide reasonable assurance of their safety and effectiveness. The three categories of devices are class I (general controls), class II (special controls), and class III (premarket approval).

The 1976 amendments broadened the definition of ''device'' in section 201(h) of the act (21 U.S.C. 321(h)) to include certain articles that were once regulated as drugs. Under the 1976 amendments, Congress classified into class III all transitional devices, i.e., those devices previously regulated as new drugs, including the absorbable PDS suture. Section 520(l)(2) of the act (21 U.S.C. 360j(l)(2)) provides that the manufacturer or importer of a device classified in class III under the transitional provisions may file a petition for reclassification of the device into class I or class II. Procedures for filing and review of classification petitions are set forth in § 860.136 (21 CFR 860.136).

II. Regulatory History of the Device

Under section 520(l)(2) of the act and § 860.136, on August 25, 1999, FDA filed a petition submitted by Ethicon, Inc., requesting reclassification of the absorbable PDS suture from class III to class II. Class II devices are those devices for which the general controls by themselves are insufficient to provide reasonable assurance of safety and effectiveness, but for which there is sufficient information to establish special controls to provide such assurance, including performance standards, postmarket surveillance, patient registries, development and dissemination of guidelines, recommendations, and any other appropriate actions the agency deems necessary (section 513(a)(1)(B) of the act). FDA consulted with members of the General and Plastic Surgery Devices Panel (the Panel members) regarding reclassification of the absorbable PDS suture. The Panel members recommended that FDA reclassify the absorbable PDS suture for soft tissue approximation, including use in pediatric cardiovascular tissue where growth is expected to occur, and ophthalmic surgery, from class III to class II. The Panel members also recommended consensus standards and device-specific labeling as the special controls that could reasonably assure the safety and effectiveness of the device.

III. FDA's Conclusion

FDA considered the Panel members' recommendations that the generic type of device, the absorbable PDS suture for soft tissue approximation, be reclassified from class III to class II. After reviewing the data in the petition and after considering the Panel members' recommendations and the comments, FDA, based on the information set forth, issued an order to the petitioner on September 4, 2001, reclassifying the absorbable PDS suture, and substantially equivalent devices of this generic type, from class III to class II. Accordingly, as required under § 860.136(b)(6), FDA is announcing the reclassification of the generic absorbable PDS suture from class III (premarket approval) into class II (special controls). The special control capable of providing reasonable assurance of safety and effectiveness for this device is a guidance document entitled ''Class II Special Controls Guidance Document: Surgical Sutures; Guidance for Industry and FDA,'' which FDA is making available elsewhere in this issue of the **Federal Register**. The guidance document describes a means by which surgical suture devices may comply with the requirement of special controls for class II devices. Any firm submitting a premarket notification (510(k)) for a new PDS suture will need to address the issues covered in the special control guidance. However, the firm needs only to show that its device meets the recommendations of the guidance or in some other way provides equivalent assurances of safety and effectiveness. The special control guidance document reframes the risks identified in the PDS reclassification order to better show how the mitigating measures recommended by the guidance are associated with each risk. The clinical sequelae of the risks identified in the order and of the risks identified in the guidance are identical. FDA notes that the class II special control guidance document incorporates consensus