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November 12, 1999

By Hand Delivery

Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane
Room 1061 (HFA-305)
Rockville, Maryland 20852

Re: Citizen Petition for Clarification of Informal Policy
Requiring ANDA Suitability Petitions for Parenteral Drugs
in Different Container Sizes

Dear Sir or Madam:

A. Action Requested

This citizen petition requests that the Food and Drug Administration (FDA) clarify its informal policy of requiring suitability petitions for parenteral drugs where the only change from the listed drug is in the size of the container and not in the strength of the drug. The clarification should state that a suitability petition is required only for changes in single-dose liquid parenteral drug container sizes.

B. Statement of Grounds

1. Background

The Hatch-Waxman Amendments expanded section 505 of the Food, Drug, and Cosmetic Act (FDCA) to authorize the submission of abbreviated new drug applications

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(ANDAs). 21 U.S.C. § 355(j)(1). An ANDA must contain information to show, among other things, that the proposed drug has the same route of administration, dosage form, and strength as the listed drug. Id. § 355(j)(2)(A)(iii). An ANDA for a drug with a different route of administration, dosage form, or strength may be submitted if the change is authorized by approval of a suitability petition. Id. § 355(j)(2)(C). FDA must approve an ANDA if it contains sufficient information to show that the route of administration, dosage form, and strength of the proposed drug are the same as those of the listed drug, id. § 355(j)(4)(D), or, if a change in one or more of those characteristics has been authorized by approval of a suitability petition, the ANDA contains the information required by FDA in the letter approving the petition. Id. § 355(j)(4)(E).

FDA's implementing regulations authorize the submission of an ANDA for a drug that is "the same as a listed drug," 21 C.F.R. § 314.92(a)(1), and, for a drug "which is not identical to a listed drug in route of administration, dosage form, and strength," upon the approval of a suitability petition. Id. § 314.93(b). The regulations specify the information a suitability petition must contain. Id. § 314.93(d). If a suitability petition is approved, an ANDA for a drug with a change of the type specified may be submitted. Id. § 314.93(c). No other type of change in a drug may be authorized by a suitability petition. Id. § 314.93(a).

FDA is required to publish and maintain a list of all drugs approved under FDCA section 505. 21 U.S.C. § 355(j)(7). FDA meets this requirement by publishing the specified information in the Orange Book.¹ 21 C.F.R. § 314.3(b). The Orange Book lists drugs in categories based on their active ingredients. Within each active ingredient category, there are subcategories of drugs having the same dosage form and route of administration. Within those subcategories, drugs are subdivided by strength. For each drug/dosage form/route/strength, a reference listed drug is designated. If there is more than one approved drug in a subdivision, then therapeutic equivalence ratings appear next to each entry. Drugs rated "A" are therapeutically equivalent and may be substituted for each other.²

¹ Approved Drug Products with Therapeutic Equivalence Evaluations, 19th Ed. (1999).

² The organization and meaning of the Orange Book entries are explained in Section 2 of the Orange Book.

2. Parenteral drug containers and strengths

Parenteral drugs are available in several dosage forms, such as solutions and powders. Parenteral drugs are provided in a variety of containers, such as vials, ampules, and bottles. Some containers for parenteral drugs are "single-dose." These containers provide a quantity of active ingredient to be used at one time. Other containers are "multiple-dose." These containers provide a quantity of active ingredient to be used more than one time.

A single-dose container of a liquid parenteral drug is analogous to a dosage unit of a solid oral dosage form drug. For example, a prefilled syringe containing a solution of 20 mg of active ingredient intended to be administered at one time is similar to a 20 mg tablet of that active ingredient. A multiple-dose parenteral drug container is analogous to a container with several tablets. For example, a vial containing a solution of 500 mg of the active ingredient to be withdrawn in successive portions is similar to a 25-unit bottle of 20 mg tablets of the active ingredient.³

Drugs in solid oral dosage form are generally provided and administered as discrete dosage units. Therefore, their "strength" can be expressed as the amount of active ingredient in each dosage unit, as in the example, above, of a 20 mg tablet. The strength of a parenteral drug (as well as of other drugs not in unit dosage form) cannot, by definition, be expressed as the amount of active ingredient in each dosage unit. Rather, the strength of a parenteral drug can only be expressed as an amount of active ingredient in a specified weight or volume of the drug or, alternatively, as a percentage.

With respect to strength, therefore, the analogy between solid oral dosage form drugs and parenteral drugs must take into account the fact that containers of parenteral drugs, unlike tablets and capsules, are not "dosage units." Hence, the total content of active ingredient in a parenteral drug container does not correspond with a "strength" in the same way that the total content of active ingredient in a tablet or capsule does. To the extent that the "total content" of active ingredient in a parenteral drug container can be said to correspond with "strength," that situation exists only in the specific case of a

³ A container of a powder form of a drug for injection is accompanied by instructions for reconstitution. These instructions specify the amount of diluent to be used to attain a specific concentration of the active ingredient in the final solution. Depending on the drug, specified diluent, and instructions, the solution may be used for a single dose or for multiple doses. This petition does not address powder form parenteral drugs. All references in this petition to parenteral drugs are to liquid preparations.

single-dose container of a liquid parenteral drug. In that case, all of the contents of the container are meant to be administered at one time (immediately or over a specified time) to one patient, or, at least, are capable of being so administered, consistent with the directions for use of the product.

3. FDA's informal suitability petition policy for different container sizes of parenteral drugs

FDA has an informal policy of requiring the submission of a suitability petition to obtain authorization for an ANDA for a parenteral drug in a drug-container size (or volume) in which the total content of the container is different from the total content of a container approved for the listed drug or in a previous suitability petition for an ANDA. This policy applies notwithstanding that there is no change in the concentration of the parenteral drug.

We do not know the specific elements of this informal policy. The existence of the policy has been publicly referred to by FDA staff but, to our knowledge, the policy has never been reduced to writing or publicly explained by the agency. The only evidence of what the policy consists of is indirect, in the form of suitability petitions filed by persons who believe, or have been advised by FDA, that a petition is necessary.

On the evidence of the suitability petitions accepted and acted on by FDA, the agency's policy is to require suitability petitions for different-size parenteral drug containers containing the same concentration of drug, irrespective of whether a container is a single-dose or a multiple-dose container. Recent examples of approved suitability petitions include 98P-0649 for daunorubicin hydrochloride 5 mg/ml in a 10 ml single-dose vial referencing a 4 ml single-dose vial and 92P-0355 for etoposide 20 mg/ml in a 12.5 ml multiple-dose vial referencing a 5 ml multiple-dose vial.

4. FDA is not authorized to require suitability petitions for different container sizes of parenteral drugs

a. FDA's definition of drug "strength." FDA is required to accept and approve an ANDA containing information that shows that the route of administration, dosage form, and strength of the proposed drug are "the same as that of the listed drug." 21 U.S.C. §§ 355(j)(2)(A)(iii), (j)(4)(D)(i). FDA may require a suitability petition for an ANDA only if the proposed drug is "different" in its route of administration, dosage form, or strength. *Id.* §§ (j)(2)(C), (j)(4)(D)(ii). The term "strength," and the terms "same" and "different" in relation to "strength," are not defined in the Hatch-Waxman provisions of the statute. They are derived from FDA's statement in a 1983 Federal Register document issuing the predecessor of 21 C.F.R. § 314.92, which sets forth the conditions under which an ANDA can be submitted. See H.R. Rep.

No. 98-857 at 21 n.3 (1984) (Attachment 1). Under the former regulation, FDA would accept an ANDA only for a drug that was “the same in active ingredient, dosage form and strength, route of administration, and conditions of use” as a drug subject to a DESI-effectiveness finding. “Abbreviated New Drug Applications; Related Drug Amendments,” 48 Fed. Reg. 2751, 2755 (Jan. 21, 1983) (Final rule) (Attachment 2).

FDA’s Hatch-Waxman regulations use similar language, defining “same as” to mean “identical in active ingredient(s), dosage form, strength, route of administration, and conditions of use. . . .” 21 C.F.R. § 314.92(a)(1). In response to a comment asking FDA to define “strength” in the context of this provision, FDA said:

“Strength” refers to the amount of the product’s active ingredients and is usually expressed in terms of weight. For example, a drug that is available as a 50 milligram (mg) tablet and a 100 mg tablet has two “strengths.”

“Abbreviated New Drug Application Regulations,” 57 Fed. Reg. 17950, 17956 (April 28, 1992) (Final rule) (Attachment 3).

This explanation equates “strength” with the amount of active ingredient in a dosage unit of a solid oral dosage form drug. The explanation thus uses the special case in which the drug is provided in unit dosage form, and the “strength” of the drug corresponds with the amount of active ingredient in the dosage unit.

Consistent with this explanation, the origin of the 1983 regulation makes clear that “strength,” as used in the 1984 statute and in the 1992 regulation, refers to the amount of active ingredient in the dosage unit of a solid oral dosage form drug or in a stated amount of the total drug, and not to the total amount of active ingredient in a container of drug not in unit dosage form. As proposed, the 1983 regulation provided that an ANDA was suitable only if the generic product was “the same in dosage form, route of administration, kind and amount of active ingredient, indication(s), and any other conditions of use as the” approved DESI drug. 43 Fed. Reg. 39126, 39129 (Sept. 1, 1978) (Attachment 4). This language was adopted from FDA’s just-issued bioequivalence regulations, 42 Fed. Reg. 1624, 1634 (Jan. 7, 1977) (Attachment 5), which defined “pharmaceutical equivalents” as “drug products that contain identical amounts of the identical active drug ingredient . . . in identical dosage forms,” the same language as in the proposed bioequivalence regulations. 40 Fed. Reg. 26164, 26165 (June 20, 1975) (Attachment 6).

The 1975 proposed bioequivalence regulations, in turn, were based on the NDA regulations then in effect. The NDA regulations required that both NDAs and ANDAs contain information describing the composition of the drug, consisting of “the name and amount of each ingredient, whether active or not, contained in a stated quantity of the

drug in the form in which it is to be distributed.” Former 21 C.F.R. § 314.1(c)(2) (item 7) (NDA) (Attachment 7) and id. § 314.1 (f)(1)(i) (ANDA) (Attachment 8). The requirement for NDAs added the parenthetical illustration “for example, amount per tablet or per milliliter.” A statement of the amount of active ingredient per unit of drug quantity was, then as now, defined as the “strength” of a drug in the drug GMP regulations. Compare former 21 C.F.R. § 210.3(d)(8)(i) (Attachment 9) with current 21 C.F.R. § 210.3(b)(16)(i).

Although the cited provisions of the NDA regulations were replaced in 1985 (see 50 Fed. Reg. 7452 (Feb. 22, 1985)), they clearly served as the basis for the suitability petition regulation issued in 1983 and, therefore, of the suitability petition provision of the Hatch-Waxman statute. The 1983 regulation replaced “identical amounts” of active ingredient, the language of the 1978 proposal, with “identical in . . . strength.” “Strength,” therefore, means identical amounts of active ingredient “in a stated quantity of the drug in the form in which it is to be distributed” – such as “amount per tablet or per milliliter.”

Conversely, the NDA regulations in effect when FDA’s original suitability petition procedure was issued, as well as the bioequivalence regulations, treated drug container size as entirely distinct from the strength of a drug. The NDA regulations required a statement of drug strength in item 7 of the NDA, but separately required information about containers, and the stability of drugs in various containers (including any “proposed multiple-dose container”), in items 8i and 8p – parts of the NDA that had nothing to do with the strength or composition of the drug. Similarly, in rejecting a comment on the proposed bioequivalence regulations that “drug product” should be defined to include “the active drug ingredient, the labeling, and the final package in which the product is distributed,” FDA stated:

The purpose of the bioequivalence regulations is to assure that pharmaceutical equivalents or pharmaceutical alternatives have equivalent bioavailability. The container and labeling have no bearing on this purpose.

42 Fed. Reg. 1624, 1626 (Jan. 7, 1977) (Attachment 10).

In sum, the “strength” of a drug for NDA and ANDA purposes is determined by the amount of active ingredient in a stated quantity of the drug, such as a dosage unit of the drug, or a specified weight or volume of the drug, and is not determined by the total content of active ingredient in the container in which a non-unit-dosage-form drug is distributed.

As noted above, defining drug “strength” as the amount of active ingredient in a specified unit – of dosage, volume, or weight – is the same as the definition of “strength” in the GMP regulations. The word “strength” is defined there as:

The concentration of the drug substance (for example, weight/weight, weight/volume, or unit dose/volume basis). . . .

21 C.F.R. § 210.3(b)(16)(i). (For ingredients that are not well characterized, “strength” refers to “potency.” 21 C.F.R. § 210.3(b)(16)(ii).) The GMP regulations are based on the statutory requirement that, to avoid being considered adulterated, a drug must be manufactured so as to have, among other attributes, “the identity and strength . . . which it purports or is represented to possess.” 21 U.S.C. § 351(a)(2)(B). The GMP definition equates “strength” with the amount of active ingredient in a specified amount of drug substance, not with the total amount of active ingredient.

b. Parenteral drug “strength.” It is possible to package a parenteral product in a container whose volume corresponds with the dosage unit, similar to a tablet consisting of the desired amount of active ingredient. Thus, a single-dose liquid parenteral drug container corresponds with a unit dosage of a solid oral dosage form drug. Multiple-dose containers of parenteral drugs, however, are commonly used to package quantities of parenteral drugs that do not correspond with a dosage unit. Multiple-dose parenteral drug containers having the same drug concentration can include an amount of active ingredient that is more or less than the amount to be administered. The distinguishing feature of a multiple-dose parenteral drug container is that it does not contain the amount of drug that is to be administered at one time – a dosage unit – but, instead, an amount that is available to the physician or pharmacist to create a dosage unit, either by using a portion of the contained amount or by combining the contained amount with all or part of the contents of additional containers of the same drug.

The “strength” of a parenteral drug is not determined by the volume of a multiple-dose container, any more than the “strength” of a tablet is determined by the number of tablets in a 100- or 1,000-unit bottle. Rather, the strength of a parenteral drug in a multiple-dose container is the concentration or percentage of the active ingredient in the total amount of drug.

c. U.S. Pharmacopeia (USP) definition of drug “strength.” This conclusion – that drug “strength” is an amount of active ingredient per unit – is consistent with FDA’s GMP definition of “strength” for drugs not formulated as dosage units. It is also supported by the USP, which states, under the heading “amount of ingredient per dosage unit,” that:

Pharmacopieal drug products not in unit dosage form shall be labeled to express the quantity of each active ingredient in each milliliter or in each gram, or to express the percentage of each such ingredient. . . .

USP 24 at 12 (Attachment 11). This requirement makes clear that the “strength” of parenteral drugs in multiple-dose containers is the concentration of the active ingredient, not the labeled amount of active ingredient in the container. See also USP 24 at 1776 (Attachment 12) (label of liquid preparation parenteral drug must state percentage content of drug or amount of drug in a specified volume).

The USP further defines “multiple-unit container” as one “that permits withdrawal of successive portions of the contents without changing the strength, quality, or purity of the remaining portion,” and a “multiple-dose container” as a “multiple-unit container for articles intended for parenteral administration only.” Id. at 11 (Attachment 13) (emphasis added). The USP thus considers “strength” to be independent of the total drug content of a container when a parenteral drug is packaged in a multiple-dose container. The USP should be dispositive on this point. The USP is an “official compendium,” 21 U.S.C. § 321(j), for purposes of the drug adulteration and misbranding provisions of the FDCA. A drug is adulterated if its “strength” differs from the standards set forth in the USP. 21 U.S.C. § 351(b). A drug is misbranded if it is not “packaged and labeled as prescribed” in the USP. 21 U.S.C. § 352(g). The USP provisions quoted above establish that the “strength” of parenteral drugs, and other non-unit-dosage form drugs, is not determined by the total active ingredient content of different-size containers of those drugs.

d. FDA regulation of drug “strength.” Other than for suitability petitions, FDA itself does not regulate different total contents of parenteral drugs containing the same concentration of drug in different size containers as “different strength” drugs.

Orange Book. The Orange Book lists different “strengths” of drugs as separate entries. For example, oral tablets of chlorpropamide are approved in 100 mg and 250 mg strengths. A tablet of chlorpropamide is one dosage unit. The Orange Book listing for this drug has separate entries for each strength of the reference chlorpropamide tablet and for each strength of each generic chlorpropamide tablet. Similarly, furosemide tablets are listed in the Orange Book with strengths of 20, 40, and 80 mg per tablet.

For parenteral drugs, the Orange Book listings vary, but they are consistent with the principle that the “strength” of a parenteral drug is the concentration of the active ingredient, not the total drug content of a container of the drug. For example, metoclopramide injection is approved at a concentration of 5 mg per ml. This drug is

available in the marketplace in container sizes of 2, 10, 30, 50, and 100 ml.⁴ These container sizes are not shown as separate entries in the Orange Book. Furosemide injection is listed in the Orange Book as only one strength, 10 mg/ml. Yet the container sizes in the marketplace are 2, 4, and 10 ml,⁵ with no Orange Book entries corresponding with these container sizes. Cimetidine injection is listed as approved in a 300 mg/2 ml strength but is available in both 2 ml and 8 ml vials,⁶ with no Orange Book entry directly specifying the 2 ml container size,⁷ or specifying the 8 ml container size at all.

On the basis of the Orange Book listings for parenteral drugs, therefore, FDA does not view the total active ingredient content of a container as corresponding with “strength.” Under FDA’s interpretation of FDCA section 505, each “strength” of a drug is a separate “approved drug” and therefore, under the statute, must be listed in the Orange Book as such. This is more than mere bookkeeping. The Orange Book is the official list of approved drug products, required to be established and updated by the FDCA. It serves as a Congressionally-mandated government notice to the public, companies, pharmacists, physicians, and formulary committees. It is the basis for decisions regarding the development of generic products, the prescribing and dispensing of equivalent drugs, and the acquisition of drug products by health care institutions. Failure to list different “strengths” of a drug product in the Orange Book is inconsistent with the statutory mandate that all approved drugs be listed, and undermines the purpose of the Orange Book to communicate information about “therapeutically equivalent

⁴ Drug Facts and Comparisons at 1559 (1999 Ed.) (Attachment 14). Several companies have more than one entry for metoclopramide injectable products. These entries may correspond with vial sizes other than those approved for the reference drug. But those different vial sizes are not specified. Therefore, they cannot be different “strengths” within the Orange Book meaning of that term. Even if the vial sizes were specified, they would be an artifact of the suitability petition policy we seek to have clarified, not of any separate standard or definition of parenteral drug “strength” as equivalent to the size of the container.

⁵ Id. at 723 (Attachment 15).

⁶ Id. at 2090 (Attachment 16).

⁷ The Orange Book entries for injectable cimetidine specify 300 mg/2 ml. This is a proportion, corresponding with conventional “strength” listings for ready-to-use parenteral solutions as concentrations of active ingredient in a volume of total drug. It does not specify that the size of a container of injectable cimetidine is 2 ml.

drugs.” Therapeutic equivalence cannot exist unless products are pharmaceutical equivalents, which includes having the “same strength.” See Letter from J. Woodcock, M.D., to H. Moore and K. Parr, Dec. 4, 1998 (98P-0547) at 3, heading (“Each strength of a listed drug product is itself a listed drug”) (Attachment 17).

The fact that FDA does not systematically specify and separately list all parenteral drugs by the total amount of drug in each container means that the agency does not view total content of a container as the “strength” of the parenteral drug packaged in that container. If FDA believed that the total content of a parenteral drug container was equivalent to “the strength” of the drug, then the agency would specify, and separately list, each parenteral container size for purposes of meeting the statutory requirement that FDA list “each drug which has been approved” and of satisfying the Orange Book’s stated function of providing “therapeutic equivalence” ratings.

If FDA were to formally adopt the position that different parenteral container sizes are different “strengths,” it could address the Orange Book requirement for listing “each strength” by revising all parenteral drug listings to specify all permissible drug-container configurations and sizes. This would not make the agency’s interpretation correct, but it would, at least, eliminate the inconsistency between the Orange Book (container size is not a “strength”) and the informal suitability petition policy (container size is a “strength”).⁸

Substitution. Different “strengths” of a drug cannot be substituted for each other. This is because different strengths are not pharmaceutically equivalent. The Orange Book listings categorize drugs on the basis of pharmaceutical equivalence, as well as bioequivalence, to facilitate substitution decisions.

The Orange Book listings for parenteral products do not systematically categorize parenteral products on the basis of container size, or even identify the approved container

⁸ For consistency’s sake, a similar expansion of Orange Book listings would be necessary for all drug products not sold as dosage units. This would include ointments, gels, creams, lotions, and inhalers. Suitability petitions would likewise be required for each container size of these non-unit-dosage form products. See, e.g., nystatin cream and ointment, approved as a ratio of 100,000 units per gram, with the container size unspecified, and available in both 15 gm and 30 gm containers. Drug Facts and Comparisons at 3145 (Attachment 18). There is no more – or less – basis for requiring suitability petitions for these differing “strength (total drug content)” containers than for differing container sizes of parenteral drug products that have no relationship to a dosage unit.

size of a particular company's product. Consequently, parenteral products within a given pharmaceutical equivalence "strength" category based on concentration are substitutable for each other, irrespective of the size of the containers in which they are packaged. Therefore, different parenteral drug container sizes are not different parenteral drug "strengths."

CDER Guidance. Guidance and other official documents issued by the Center treat the "strength" of a drug as different from, and not determined by, the size and fill of the container in which the drug is packaged. The Office of Generic Drugs (OGD) guidance titled "Variations in Drug Products that May Be Included in a Single Abbreviated New Drug Application" [date] states that "[d]ifferent strengths or concentrations of a drug product" may be submitted in "one original application. . . ." Section IIF (Attachment 19). Separately, the guidance states that "products utilizing different container sizes, configurations, and materials . . . of one finished pharmaceutical product . . . may usually be included in a single application." Section IIG (Attachment 19). The Guidance discusses "strengths or concentrations" as a different attribute of a drug from "container sizes." Moreover, under "specific dosage forms," this guidance states that one ANDA for a parenteral solution or suspension product may include "one formulation/one strength/multiple fill sizes" but that more than one ANDA is necessary where there is "one formulation/one strength/one or more multiple fill sizes/multiple packaging types or container materials." Section IIIB (Attachment 20). The matrix is, therefore, based on the assumption that "strength" and "fill size" are not the same. The narrative for this matrix also assumes that "strength" and "fill size" are distinct from each other (referencing "varying fill volumes (e.g., 2, 5, and 20 mL vial sizes)" in connection with "one strength" and "multiple fill sizes").

The CDER Manual of Policies and Procedures (MAPP) contains a directive to reviewers titled "Consistent Information in an Abbreviated Application," MAPP 5225.2 (Nov. 1, 1995) (Attachment 21). This directive explains what information an ANDA must contain about container/closure systems to support OGD review of the product and to provide a basis for an accurate "How Supplied" section of the approved ANDA labeling. The "How Supplied" section must contain, "[i]n addition to information on the batch number and strength of the drug product used, [etc.], . . . the following information for each container, closure or stopper . . . 2. complete listing of all fill volumes and container sizes and how many units are contained in each." This document clearly distinguishes between "strength," on the one hand, and fill volume or container size, on the other.

User fees. The agency interprets "strength" as different from container size in determining drug product user fees: "Products that differ in strength or potency are subject to separate product fees. Products of the same strength or potency packaged in different container sizes are not subject to separate fees." User Fee Correspondence 2,

Attachment D – Application, Product, & Establishment Fees: Common Issues and Their Resolution, paragraph A9 (Revised December 16, 1994) (Attachment 22). This guidance interprets the statutory term “prescription drug product,” which “means a specific strength or potency of a drug in final dosage form.” 21 U.S.C. § 379g(3).

If the container size of a parenteral drug corresponded with the “strength” of the drug, then it would be unlawful for FDA to excuse parenteral drug products in different container sizes from separate user fees while imposing such fees on products of different “strength” or “potency.” Therefore, the “strength” of a parenteral drug is not determined by its container size or total content. Moreover, FDA’s statement that “products” can both have “the same strength or potency” and be “packaged in different container sizes” cannot be reconciled with the proposition that parenteral drugs in different container sizes are “different strengths” for purposes of requiring suitability petitions.

e. Conclusion. FDA’s informal policy of requiring a suitability petition for a different parenteral drug container size as a different “strength” under 21 U.S.C. § 355(j)(2)(C) cannot be justified as a general rule, because container size and strength do not correlate with each other in all cases. FDA is required to approve ANDAs meeting the standards of § 355(j)(2)(A). A parenteral drug that differs from the listed drug only in the size or total contents of its container does not have a different strength, and therefore it meets the requirement of § 355(j)(2)(A)(iii). To force an applicant for such a drug to submit a suitability petition violates the statutory mandate that FDA “may not require that an abbreviated application contain information in addition to that required by clauses (i) through (viii)” of § 355(j)(2)(A).

5. The policy should be clarified to apply only to single-dose liquid parenteral drug containers

Liquid parenteral drugs are supplied in multiple-dose and single-dose containers. According to the USP, a “single-dose” parenteral drug container “provides the amount specified for parenteral administration at one time” USP 24 at 1777 (Attachment 23). The “single-dose” parenteral drug container is a subcategory of the “single-unit container,” which is a container “designed to hold a quantity of drug product intended for administration as a single dose.” *Id.* at 11 (Attachment 13).

Under the USP approach, the amount of active ingredient in a “single-dose” liquid parenteral drug container could be interpreted as corresponding with “strength” as defined by FDA in the preamble to the Hatch-Waxman regulations, i.e., it is the amount of active ingredient in one “dosage unit.” It is not the position of this petition that this interpretation is necessarily correct. However, the interpretation is defensible, whereas interpreting “strength” to apply to the amount of active ingredient in all liquid parenteral drug containers, including multiple-dose containers, is not defensible. Accordingly, FDA

should, at a minimum, clarify that its suitability petition policy is limited to changes in the "total drug content" of single-dose liquid parenteral drug containers, because the size of such a container bears a rational relationship to the "strength" of the drug as determined by the amount of active ingredient in a given dosage unit of the drug. Moreover, as we understand the agency's rationale for the policy, it is only single-dose parenteral drug containers that have the risk (potential excessive dosing due to user error) the policy is intended to address. To apply the policy to multiple-dose parenteral drug containers of different sizes cannot be defended either legally or on the basis of the policy's own logic.

If the agency has additional concerns about multiple-dose parenteral drug container sizes, it should not address them by inappropriately requiring suitability petitions. It should address them by conducting an internal review of ANDAs for parenteral drugs in different multiple-dose container sizes based on the requirement that an ANDA contain information to show that the proposed generic drug has "the same conditions of use" as those of the listed drug.

The "conditions of use" interpretation has the advantage both of being more defensible on its own terms and of avoiding the unintended consequences that may result from an overly broad interpretation of the term "strength" for the purpose of justifying a suitability petition requirement that FDA believes is necessary to address issues that have nothing to do with "strength." Because the applicability of several other provisions of FDCA section 505 is based on whether or not an ANDA relates to a distinct drug product, interpreting the term "strength" – one of the defining attributes of a distinct drug product – to apply to different multiple-dose container sizes of parenteral drugs may result in the inappropriate use of these other provisions in situations where there are not, in actuality, different drug products, but only one drug product in containers of different sizes.

In any event, whether or not FDA relies on the "same conditions of use" requirement to deal with issues relating to multiple-dose liquid parenteral drug container sizes, it cannot lawfully rely on the suitability petition requirement of the Hatch-Waxman Amendments. That requirement applies only to changes in drug "strength," and other basic pharmaceutical attributes. There is simply no conceivable view of the concept of drug "strength" that applies to different multiple-dose liquid parenteral drug container sizes. For this reason, we request that FDA clarify its informal policy to limit the requirement for suitability petitions for liquid parenteral drugs with different total drug contents to those in single-dose containers.

C. Environmental Impact

A claim for categorical exclusion from the requirements for Environmental Assessment is made pursuant to 21 C.F.R. § 25.31(a).

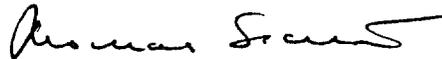
D. Economic Impact

Provided on request.

E. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Sincerely,



Thomas Scarlett

TS/sas
Attachments

LEGISLATIVE HISTORY

P.L. 98-417

[page 21]

ANDA's for drugs which are the same

In the case of drugs which are the same as the listed drug, the focus of the bill is to provide the Food and Drug Administration (FDA) with sufficient information to assure that the generic drug is the same as the listed drug² that has previously been determined to be safe and effective. Some have suggested that a generic drug must be identical in all respects to the listed drug instead of the same. The regulations that permit ANDA's for pre-1962 pioneer drugs make no such distinction.³ In rejecting the use of the term identical, the FDA regulation comments that "identical means a product that is the same in dosage form, strength, and route of administration, contains the same active ingredient, and is recommended for use under the same conditions of use."⁴ The Committee has adopted the FDA's policy of utilizing the term "same" except that the bill permits an ANDA to be approved for less than all of the indications for which the listed drug has been approved as explained below.

First, an ANDA must include sufficient information to show that the conditions of use for which the applicant is seeking approval are the same as those that have been previously approved for the listed drug. The applicant need not seek approval for all of the indications for which the listed drug has been approved. For example, if the listed drug has been approved for hypertension and angina pectoris, and if the indication for hypertension is protected by patent, then the applicant could seek approval for only the angina pectoris indication.

While the FDA's current regulations for considering ANDA's for pioneer drugs approved before 1962 permit an applicant to petition for approval for an indication other than that which has been approved for the pioneer drug, section 101 of the bill overturns that policy.⁵ Thus, an ANDA may not be considered for a condition of use that has not been previously approved for the listed drug.

An ANDA must also contain sufficient information to show that the active ingredients of the generic drug are the same as those of the listed drug. If the listed drug has one active ingredient, then the active ingredient of the generic must be the same. If the listed drug has more than one active ingredient, then sufficient information must be included to show that all of the active ingredients in the generic drug are the same.

In addition, an ANDA must contain sufficient information to show that the route of administration, the dosage form and the strength of the generic drug are the same as those of the listed drug.

Further, an ANDA must include sufficient information to show that the generic drug is bioequivalent to the listed drug.

² The term "listed drug" is explained in paragraph (6) of new section 505(j) of the FDCA. Generally, a listed drug includes any drug that has been approved for safety and effectiveness or that has been approved under new subsection (j).

³ 48 Fed. Reg. 2751 (1983).

⁴ Id. at 2753.

⁵ Id. at 2755.

21 C.F.R. 314.2(c) provides in part:

"A prospective applicant may seek a determination of the suitability of an abbreviated new drug application for a product that the applicant believes similar or related to a drug product that has been declared to be suitable for an abbreviated new drug application . . ."

under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10), Parts 310 and 314 are amended as follows:

PART 310—NEW DRUGS

1. Part 310 is amended in § 310.6 by revising the section heading, the seventh sentence of paragraph (a), and paragraphs (b) and (c), to read as follows:

§ 310.6 Applicability of "new drug" or safety or effectiveness findings in drug efficacy study implementation notices and notices of opportunity for hearing to identical, related, and similar drug products.

(a) * * * However, it is essential that the findings and conclusions that a drug product is a "new drug" or that there is a lack of evidence to show that a drug product is safe or effective be applied to all identical, related, and similar drug products to which they are reasonably applicable. * * *

(b)(1) An identical, related, or similar drug includes other brands, potencies, dosage forms, salts, and esters of the same drug moiety as well as of any drug moiety related in chemical structure or known pharmacological properties.

(2) Where experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs would conclude that the findings and conclusions, stated in a drug efficacy notice or notice of opportunity for hearing, that a drug product is a "new drug" or that there is a lack of evidence to show that a drug product is safe or effective are applicable to an identical, related, or similar drug product, such product is affected by the notice. A combination drug product containing a drug that is identical, related, or similar to a drug named in a notice may also be subject to the findings and conclusions in a notice that a drug product is a "new drug" or that there is a lack of evidence to show that a drug product is safe or effective.

(3) Any person may request an opinion on the applicability of such a notice to a specific product by writing to the Food and Drug Administration at the address shown in paragraph (e) of this section.

(c) Manufacturers and distributors of drugs should review their products as drug efficacy notices are published and assure that identical, related, or similar products comply with all applicable provisions of the notices.

* * * * *

PART 314—NEW DRUG APPLICATIONS

2. Part 314 is amended:

a. In § 314.1 by removing paragraph (f) and by revising the first sentence of paragraph (a)(1), to read as follows:

§ 314.1 Applications.

(a)(1) Applications to be filed under section 505(b) of the act shall be submitted in the form described in paragraph (c) of this section or optionally in the form described in paragraph (d) of this section and assembled as required by paragraph (e) of this section; if the drug product is one for which an abbreviated new drug application has been found by the Food and Drug Administration to be sufficient, the application may be limited to the information described in § 314.2 unless otherwise specified in such finding.

* * * * *

b. By adding new § 314.2, to read as follows:

§ 314.2 Abbreviated new drug applications.

(a) The Food and Drug Administration has determined that many drug products covered by the drug efficacy study may be approved for marketing without the submission of additional evidence of preclinical and clinical studies (other than in vivo bioavailability studies) to show safety and effectiveness. When such a finding has been made for a drug product, an abbreviated form of a new drug application is sufficient for that product.

(b)(1) The Food and Drug Administration will accept an abbreviated new drug application only if it has made a finding that an abbreviated application is suitable for the drug product.

(2) A finding by the Food and Drug Administration that an abbreviated new drug application is suitable for a drug product applies only to a product that is the same in active ingredient, dosage form and strength, route of administration, and conditions of use as the drug product that was the subject of the finding. For a drug product that is similar but different in one or more of these characteristics, an abbreviated new drug application will be accepted only if the Food and Drug Administration has made a separate finding of suitability. However, acceptance of an abbreviated new drug application for a drug product does not signify that the product is safe and effective until the application is approved.

(3) A finding that a drug product is a "new drug," because it is similar to a product that is a "new drug," and, therefore, is subject to either a full or abbreviated new drug application does not include a finding that an abbreviated application is suitable for the similar product.

(4) A finding that a single-active-entity drug product is safe and effective and that an abbreviated new drug application is suitable is not a basis for determining that a combination drug product containing that entity as one of its ingredients is either safe or effective or that an abbreviated new drug application is suitable. The finding also is not a basis for determining that the combination drug product meets all of the requirements for combination drugs as described in § 300.50 of this chapter.

(c) A prospective applicant may seek a determination of the suitability of an abbreviated new drug application for a product that the applicant believes similar or related to a drug product that has been declared to be suitable for an abbreviated new drug application. Extension of the finding that a drug product is safe and effective to another product will ordinarily be limited to other dosage forms for the same route of administration or to closely related ingredients. If preclinical or clinical evidence is needed to support the safety, or if clinical evidence is needed to support the effectiveness, of the proposed product, then an abbreviated new drug application is not suitable for the similar or related drug product.

(d) A person seeking a determination that an abbreviated new drug application is suitable for a similar or related drug product shall use the procedures established in § 10.30 of this chapter. The petitioner shall set forth the reasons that justify extending the finding that an abbreviated new drug application is suitable for one product to the similar or related product proposed to be marketed.

(e) A new drug application submitted in the form of an abbreviated new drug application for a drug product that has not been the subject of a finding that allows an abbreviated application for the product will be considered to be a petition under § 10.30 of this chapter and will be processed as such.

(f) Each abbreviated new drug application is required to contain a reference to the finding of the Food and Drug Administration that an abbreviated application is suitable for the specific product that is the subject of the application. Each abbreviated new drug application shall also contain:

established name and proprietary name, and the date of withdrawal from sale.

14. One comment asked FDA to clarify whether an applicant's obligation to submit postmarketing reports begins when FDA approves its ANDA or when the ANDA approval becomes effective.

Although the preamble to the proposed rule said proposed § 314.81 would apply upon ANDA approval regardless of the ANDA's effective date (54 FR 28872 at 28889), FDA has reconsidered this position in light of its policy on delayed effective dates and approvals. FDA does not consider a drug to be approved until the effective date of approval and regards those drug products with delayed effective dates as having tentative approvals. This policy affects § 314.81 because section 505(k) of the act authorizes reporting requirements for drug products that have an approval "in effect." Thus, an applicant's obligation to submit postmarketing reports will begin when the ANDA approval becomes effective.

15. Two comments addressed the 15-day reporting deadline in proposed § 314.81(b)(3)(iii)(a). One comment said a company "does not always know within 15 days of its last shipment that it intends to discontinue marketing a product" and "it is not always clear to a company whether a product is going to be withdrawn from marketing or just temporarily suspended." The comment would have applicants notify FDA that they will withdraw a product when they decide to permanently withdraw the product from sale. The second comment added that the existing rule's annual reporting requirement was satisfactory.

FDA believes the first comment misinterprets the provision. FDA does not expect parties to submit reports within 15 days from the date of their last shipment. The 15-day period begins from the time the firm decides to withdraw the product from the market. Such withdrawals are not limited to permanent withdrawals; FDA is interested in any decision to discontinue marketing because of the possible implications for the product's safety and efficacy. The agency also declines to replace the 15-day reporting period with an annual reporting requirement as suggested by the second comment. The withdrawal of an approved NDA drug product may affect the marketing of duplicate ANDA drug products, so timely reports of drug product withdrawals may be very important.

Section 314.92—Drug Products for Which Abbreviated Applications May be Submitted

FDA received four comments on proposed § 314.92. The proposed rule

stated that abbreviated applications are suitable for certain drug products, such as drug products that are the same as a listed drug, drug products that meet the monograph for an antibiotic drug for which FDA has approved an application, drug products for which FDA has found an ANDA to be suitable and has announced such a finding in the *Federal Register*, and drug products that FDA has declared to be suitable for an ANDA submission under the petition procedures.

16. One comment asked FDA to refuse ANDA's for DESI drugs on the grounds that the statute only applies to post-1984 ANDA's. The comment noted that DESI drugs are reviewed by category rather than active ingredient and said some DESI active ingredient categories lack a "readily identifiable pioneer NDA product." Another comment supported ANDA's for DESI drugs.

The ANDA provisions of the 1984 amendments are applicable to all generic drugs for which approval is sought after September 24, 1984, the date on which the statute was enacted. Perpetuating different ANDA systems for pre-1982 drugs and post-1982 drugs would be needlessly confusing, illogical, and inefficient to FDA, the public, and industry. Therefore, FDA has included DESI drugs in these regulations.

Upon further consideration, FDA agrees that ANDA's may be inappropriate for some DESI drug products. In the DESI process, a DESI-reviewed NDA or ANDA is usually considered approved for safety and effectiveness through the approval of a supplement that brings the NDA or ANDA drug product into compliance with a DESI-upgrade notice. The DESI-upgrade notice describes what information the NDA or ANDA holder must provide in order for its drug product to be considered effective. If the NDA or ANDA holder complies with the notice through an approved supplement, then the drug product is considered to be safe and effective and can be listed in the *Orange Book*. Once this occurs, a person may be able to submit an ANDA for the product. However, if the NDA or ANDA holder fails to comply with the notice, the NDA or ANDA drug product is not considered to be approved for effectiveness and cannot be a listed drug. Under these circumstances, an ANDA cannot be submitted because there is no "listed drug." Therefore, FDA has revised § 314.92 by removing paragraph (a)(3) and renumbering paragraph (a)(4) as (a)(3). An applicant seeking to rely on the findings reflected in a DESI-upgrade notice, in the absence of a listed drug, should submit its

application under section 505(b)(2) of the act.

Once a drug subject to a DESI notice is approved for safety and effectiveness and can serve as a listed drug, the agency will require the submission of an ANDA under section 505(j) of the act for a generic version of the product. As a matter of policy, the agency does not accept applications under section 505(b)(2) of the act when there is a listed drug that would provide a basis for an application under section 505(j) of the act. For clarity, FDA has added a new paragraph (d)(9) in § 314.101. The issue had been discussed in the preamble to the proposed rule (54 FR 28890 through 28891). At that time, the agency proposed to treat a 505(b)(2) application as submitted under section 505(j) of the act if the application was for a duplicate of a listed drug eligible for approval under section 505(j) of the act. Id. FDA believes that the policy it is describing in new § 314.101(d)(9), that an application for a drug such as this needs to be submitted by the applicant as an ANDA under section 505(j) of the act, is the preferable approach.

17. Two comments concerned proposed § 314.92(a)(1), which said, in part, that an ANDA would be suitable for a drug product that is the same as a listed drug and that the term "same as" means "identical in active ingredient(s), dosage form, strength, route of administration, and conditions of use, except that conditions of use for which approval cannot be granted because of exclusivity or an existing patent may be omitted." The proposed rule would also require potential applicants to comply with § 314.122, "Submitting an abbreviated application for, or a 505(j)(2)(C) petition that relies on, a listed drug that is no longer marketed," if the listed drug had been voluntarily withdrawn or not offered for sale by its manufacturer. One comment asked FDA to define "strength." The second objected to the language on voluntary withdrawals. The comment said NDA holders should disclose the reasons for withdrawing a product, and FDA should determine whether those reasons raise safety or efficacy questions, and then give ANDA holders an opportunity to examine and respond to the information on the withdrawal.

"Strength" refers to the amount of the product's active ingredient and is usually expressed in terms of weight. For example, a drug that is available as a 50 milligram (mg) tablet and a 100 mg tablet has two "strengths."

As for voluntary withdrawals and the reasons for a withdrawal, FDA refers

a. By revising the first sentence of § 314.1(a)(1) to read as follows:

§ 314.1 Applications.

(a)(1) Applications to be filed under section 505(b) of the act shall be submitted in the form described in paragraph (c) of this section or optionally in the form described in paragraph (d) of this section and assembled as required by paragraph (e) of this section; if the drug is one for which an abbreviated new drug application has been found by the Food and Drug Administration to be sufficient, the application may be limited to the information described in § 314.3 unless otherwise specified in such finding. . . .

b. By redesignating § 314.1(f) as § 314.3, and revising it to read as follows:

§ 314.3 Abbreviated applications.

(a) The Commissioner of Food and Drugs has determined that many drug products covered by the drug efficacy study may be approved for marketing without the submission of additional evidence of preclinical and clinical studies to show safety and effectiveness. When such a determination has been made for a drug product, an abbreviated form of a new drug application is sufficient for that product.

(b) A finding by the Commissioner of Food and Drugs that an abbreviated new drug application is appropriate for a drug product is limited to products that are the same in dosage form, route of administration, kind and amount of active ingredient, indication(s), and any other conditions of use as the drug product that was the subject of the finding. A determination that an abbreviated new drug application is the appropriate form of application for a drug product does not apply to a similar or related drug product unless the notice of that finding specifies that it applies to a particular similar or related product and that product is described.

(c) A prospective applicant may seek a determination of the acceptability of an abbreviated new drug application for a product that the applicant believes similar or related to a drug product that has been declared to be eligible for abbreviated new drug application submissions. Extension of the finding that a drug product is safe and effective to another product will ordinarily be limited to other dosage forms for the same route of administration or to closely related ingredients. If preclinical or clinical evidence is needed to support the safety, or if clinical evidence is needed to support the effectiveness, of the proposed product, then an abbreviated new drug

application is not appropriate for the similar or related drug product.

(d) A person seeking a determination that an abbreviated new drug application is appropriate for a similar or related drug product shall use the procedures established in § 10.30 of this chapter. The petitioner shall set forth the reasons that justify extending the finding that an abbreviated new drug application is appropriate for one product to the similar or related product proposed to be marketed.

(e) A new drug application submitted in the form of an abbreviated new drug application for a drug product that has not been the subject of a finding that allows an abbreviated application for the product will be considered to be a petition under § 10.30 of this chapter and will be processed as such.

c. By adding to § 314.110 new paragraph (f) to read as follows:

§ 314.110 Reasons for refusing to file applications.

(f) An application submitted in the form of an abbreviated new drug application in the absence of a prior finding that the abbreviated form of a new drug application is appropriate for the drug product, as required by § 314.3, will not be accepted as an application within the meaning of section 505(b) of the act. It will be considered as a petition, under § 10.30 of this chapter, for a determination on the acceptability of abbreviated new drug applications for the product.

Interested persons may, on or before October 11, 1978, submit to the Hearing Clerk (HFA-305), Food and Drug Administration, Room 4-65, 5600 Fishers Lane, Rockville, Md. 20857, written comments regarding this proposal. Four copies of all comments shall be submitted, except that individuals may submit single copies of comments, and shall be identified with the Hearing Clerk docket number found in brackets in the heading of this document. Received comments may be seen in the above office between the hours of 9 a.m. and 4 p.m., Monday through Friday.

NOTE.—The Food and Drug Administration has determined that this proposal will not have a major economic impact as defined by Executive Order 11821 (amended by Executive Order 11949) and OMB Circular A-107. A copy of the economic impact assessment is on file with the Hearing Clerk, Food and Drug Administration.

Dated: August 22, 1978.

SHERWIN GARDNER,
Acting Commissioner of
Food and Drugs.

[FR Doc. 78-24472 Filed 8-31-78; 8:45 am]

[4210-01]

DEPARTMENT OF HOUSING AND URBAN DEVELOPMENT

Federal Insurance Administration

[24 CFR Part 1917]

[Docket No. F1-4457]

NATIONAL FLOOD INSURANCE PROGRAM

Proposed Flood Elevation Determination for the City of Merced, Merced County, Calif.

AGENCY: Federal Insurance Administration, HUD.

ACTION: Proposed rule.

SUMMARY: Technical information or comments are solicited on the proposed base (100-year) flood elevations listed below for selected locations in the city of Merced, Merced County, Calif. These base (100-year) flood elevations are the basis for the flood plain management measures that the community is required to either adopt or show evidence of being already in effect in order to qualify or remain qualified for participation in the national flood insurance program (NFIP).

DATE: The period for comment will be ninety (90) days following the second publication of this proposed rule in a newspaper of local circulation in the above-named community.

ADDRESS: Maps and other information showing the detailed outlines of the flood-prone areas and the proposed base (100-year) flood elevations are available for review at the City Hall, 561 West 18th Street, Merced, Calif. Send comments to: Mr. Allann Schell, City Manager, City of Merced, P.O. Box 2068, Merced, Calif. 95340.

FOR FURTHER INFORMATION CONTACT:

Mr. Richard Krimm, Assistant Administrator, Office of Flood Insurance, Room 5270, 451 Seventh Street SW., Washington, D.C. 20410, 202-755-5581 or toll-free line 800-424-8872.

SUPPLEMENTARY INFORMATION: The Federal Insurance Administrator gives notice of the proposed determinations of base (100-year) flood elevations for the city of Merced, Calif., in accordance with section 110 of the Flood Disaster Protection Act of 1973 (Pub. L. 93-234), 87 Stat. 980, which added section 1363 to the National Flood Insurance Act of 1968 (Title XIII of the Housing and Urban Development Act of 1968 (Pub. L. 90-448)), 42 U.S.C. 4001-4128, and 24 CFR 1917.4(a).

These elevations, together with the flood plain management measures required by § 1910.3 of the program regulations, are the minimum that are re-

FDA are determined to be trade secrets under § 320.61 FDA is precluded from disclosing these data and information. If the data and information identify a bioequivalence problem, however, protection of the public health requires FDA to take regulatory action to remedy the problem. The Commissioner believes it is inconsistent with due process to issue a proposed bioequivalence requirement on the basis of "secret data and information" that interested persons can neither see nor comment upon. Therefore, FDA will release a summary of these data and information (see paragraph 47) at the time a proposed bioequivalence requirement is published in the FEDERAL REGISTER. The Commissioner concludes that the comment's proposal to delay finalizing these regulations for further consideration of the procedural question is inconsistent with the public interest. The Commissioner, however, invites any interested person to submit a petition proposing a change in these regulations to prohibit the disclosure of analytical methods to determine bioequivalence. The Commissioner also requests that Congress reconsider whether any safety and effectiveness data, including bioequivalence data and methodology, should be treated as trade secrets.

OLD DRUG MONOGRAPHS

50. One comment concerning proposed § 320.3(o) (now § 320.60) stated that it is assumed that the yet-to-be-formalized old drug monograph concept will include a bioequivalence requirement for such monographed drug.

The Commissioner advises that, one of the approaches to old drug monographs now under consideration in FDA would provide that, if an old drug monograph is established for a drug product for which a bioequivalence requirement has been established, the monograph will include a requirement for bioequivalence testing.

MARKETING PRODUCTS THAT DO NOT MEET AN IN VITRO STANDARD

51. Several comments regarding proposed § 320.3(p) (now § 320.61) questioned why a manufacturer whose product does not meet an in vitro bioequivalence standard must, in lieu of reformulation to meet the standard, demonstrate that his product is bioavailable by in vivo testing of three consecutive batches of the drug product. The comments noted that one lot testing is apparently satisfactory if the product meets the in vitro bioequivalence standard, while in vivo testing is specific, absolute, and represents the primary standard of bioavailability; therefore, the comments suggested that in vivo testing be required for only one batch.

The Commissioner is of the opinion that in vivo testing of a single batch of a drug product that fails to meet an in vitro bioequivalence standard established through correlation with in vivo data is not sufficient to assure batch-to-batch uniformity. Therefore, if a drug product does not meet an in vitro bioequivalence standard, the manufacturer has the option of either reformulating the product

to meet the standard or testing three consecutive batches in vivo to demonstrate bioequivalence and batch-to-batch uniformity. The option for in vivo testing was included in proposed § 320.3(p) because the Commissioner recognizes that, occasionally, a drug product that fails to meet an in vitro bioequivalence standard will nonetheless be shown to be bioequivalent when tested in vivo. This is because the in vitro bioequivalence standard is designed to identify and screen out all batches that may not be bioequivalent. In selecting the standard, FDA must, if necessary for protection of the public health, err in favor of a standard that may result in the failing of a few batches that are later shown to be bioequivalent when tested in vivo rather than a standard that may result in the passing of a few batches that are shown not to be bioequivalent when tested in vivo. The Commissioner advises that proposed § 320.3 (1) (now § 320.56) requires that if a bioequivalence requirement specifies an in vitro bioequivalence standard, the manufacturer shall conduct the test on a sample of each batch to assure batch-to-batch uniformity. Thus, one lot testing is not satisfactory if the bioequivalence requirement is an in vitro bioequivalence standard.

Requirements for in vivo testing of a drug product not meeting an in vitro bioequivalence standard proposed in § 320.3 (p) have been revised for clarity and are in § 320.61 of the final regulations.

The Commissioner has carefully considered the environmental effects of the regulations and, because the action will not significantly affect the quality of the human environment, has concluded that an environmental impact statement is not required. The Commissioner has also carefully considered the inflation impact of the regulations as required by Executive Order 11821, OMB Circular A-107, and Guidelines issued by the Department of Health, Education, and Welfare, and no major inflation impact has been found. Copies of FDA environmental and inflation impact assessments are on file with the Hearing Clerk, Food and Drug Administration.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(p), 502, 505, 701(a), 52 Stat. 1041-1042 as amended, 1050-1053 as amended, 1055 (21 U.S.C. 321(p), 352, 355, 371(a)) and under authority delegated to the Commissioner (21 CFR 5.1) (recodification published in the FEDERAL REGISTER of June 15, 1978 (41 FR 24262)), Chapter I of Title 21 of the Code of Federal Regulations is amended as follows:

1. In Part 314:

a. By adding to § 314.111 new paragraph (a)(8) to read as follows:

§ 314.111 Refusal to approve the application.

(a)

(8) The applicant fails to submit bioavailability or bioequivalence data required under Part 320 of this chapter.

.

b. By adding to § 314.115 new paragraph (c)(5) to read as follows:

§ 314.115 Withdrawal of approval of application.

(c)

(5) That the applicant has failed to submit bioavailability or bioequivalence data required under Part 320 of this chapter.

2. By adding new Part 320 consisting at this time of Subparts A and C to read as follows:

	Subpart A—General Provisions
Sec	
320.1	Definitions
	Subpart B—[Reserved]
	Subpart C—Bioequivalence Requirements
320.50	Purpose.
320.51	Procedures for establishing or amending a bioequivalence requirement.
320.52	Criteria and evidence to establish a bioequivalence requirement.
320.53	Types of bioequivalence requirements.
320.54	Contents of a petition to establish a bioequivalence requirement.
320.55	Requirements for batch testing and certification by the Food and Drug Administration.
320.56	Requirements for in vitro testing of each batch.
320.57	Requirements for the conduct of in vivo bioequivalence testing in humans.
320.58	Requirements for marketing a drug product subject to a bioequivalence requirement.
320.59	Bioequivalence requirements based on data voluntarily submitted.
320.60	Bioequivalence requirements for a drug product subject to an old drug monograph.
320.61	Requirements for in vivo testing of a drug product not meeting an in vitro bioequivalence standard.
320.62	Requirements for maintenance of records of bioequivalence testing.

AUTHORITY: Secs. 201(p), 502, 505, 701(a) 52 Stat. 1041-1042 as amended, 1050-1053 as amended, 1055 (21 U.S.C. 321(p), 352, 355, 371(a)), unless otherwise noted.

Subpart A—General Provisions

§ 320.1 Definitions.

(a) [Reserved]

(b) "Drug product" means a finished dosage form, e.g., tablet, capsule, or solution, that contains the active drug ingredient, generally, but not necessarily in association with inactive ingredients.

(c) "Pharmaceutical equivalents" means 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.

(d) "Pharmaceutical alternatives" means drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same

of an approved new drug application, or is identical, similar, or related to such a drug product, an IND shall be submitted only for:

(i) A single dose study in normal subjects or patients where the dose exceeds that specified in the labeling of the drug product which is the subject of an approved new drug application.

(ii) A steady-state study in patients where the dose exceeds that specified in the labeling of the drug product which is the subject of an approved new drug application.

(iii) A steady-state study in normal subjects whether or not the dose exceeds that specified in the labeling of the drug product which is the subject of an approved new drug application.

(3) The provisions of § 312.1 of this chapter are applicable to any bioavailability study conducted under an IND. Written informed consent is required pursuant to § 310.102 of this chapter.

(f) General inquiries relating to in vivo bioavailability requirements and methodology shall be submitted to the Food and Drug Administration, Bureau of Drugs, Division of Biopharmaceutics (HFD-520), 5600 Fishers Lane, Rockville, MD 20852.

Interested persons may, on or before August 4, 1975, submit to the Hearing Clerk, Food and Drug Administration, Rm. 4-85, 5600 Fishers Lane, Rockville, MD 20852, written comments regarding this proposal. Comments shall be filed in quintuplicate and shall be identified with the Hearing Clerk docket number found in the document heading. Received comments may be seen in the above office during working hours, Monday through Friday.

Dated: June 13, 1975.

A. M. SCHMIDT,
Commissioner of Food and Drugs.

[FR Doc.75-15966 Filed 6-19-75; 8:45 am]

[21 CFR Parts 314 and 320]

[Docket No. 75N-0060]

PROCEDURES FOR ESTABLISHING A BIOEQUIVALENCE REQUIREMENT

Notice of Proposed Rule Making

The Commissioner of Food and Drugs is proposing procedures for establishing a bioequivalence requirement when there is evidence that drug products containing the same therapeutic moiety and intended to be used interchangeably for the same therapeutic effect are not or may not be bioequivalent. The Commissioner also proposes to define certain terms relating to bioequivalence. In addition, the Commissioner proposes to amend the regulations to specify that failure to submit required bioavailability or bioequivalence data shall be reason for refusal to approve, or to withdraw approval of, a new drug application. Interested persons have until August 4, 1975, to submit comments.

In the FEDERAL REGISTER of January 5, 1973 (38 FR 885), the Commissioner proposed regulations regarding bioavailability requirements for prescription drugs.

Since that time, there has been a great deal of discussion in the Food and Drug Administration, Congress, the drug industry, and medical and scientific communities regarding evidence that certain drug products, which are intended to be used interchangeably for the same therapeutic effect, have produced clinically important and measurable differences in the therapeutic effect, and that these differences were the result of differences in the bioavailability of these drug products.

Since the January 5, 1973 proposal, there have been numerous reports, symposia, and publications from academic institutions, industry, professional groups such as the Academy of Pharmaceutical Sciences, and organizations such as the National Academy of Sciences and the World Health Organization dealing with the subject of drug bioavailability. The Food and Drug Administration has participated in several symposia and meetings, some of which were cosponsored by the Agency, dealing with the subject of bioavailability of new drugs, old drugs, and antibiotics. From such meetings and discussions have evolved the definitions of problems and procedures for their solutions proposed in this document. These definitions and concepts have been shared with the Drug Bioequivalence Study Panel, the Bioequivalence Task Force of the Academy of Pharmaceutical Sciences, and biopharmaceutical experts and have been included in congressional testimony and speeches.

Beginning on April 12, 1974, the Drug Bioequivalence Panel formed by the Congress of the United States, Office of Technology Assessment (OTA), began to examine the relationships between the chemical and therapeutic equivalence of drug products and to assess the capability of current technology—short of therapeutic trials in man—to determine whether drug products with the same physical and chemical composition produce comparable therapeutic effects. On July 15, 1974, the OTA released the panel's conclusions and recommendations in a report entitled "Drug Bioequivalence." Among the conclusions and recommendations contained in the report were the following:

1. Current standards and regulatory practices do not ensure bioequivalence of drug products.

2. Variations in the bioavailability of drug products have been recognized as responsible for a few therapeutic failures. It is probable that other therapeutic failures (or toxicity) of a similar origin have escaped recognition.

3. Most of the analytical methodology and experimental procedures for the conduct of bioavailability studies in man are available. Additional work may be required to develop means of applying them to certain drugs and to special situations of drug use.

4. It is neither feasible nor desirable that studies of bioavailability be conducted for all drugs or drug products. Certain classes of drugs for which evidence of bioequivalence is critical

should be identified. Selection of these classes should be based on clinical importance, ratio of therapeutic to toxic concentration in blood, and certain pharmaceutical characteristics.

5. Additional research aimed at improving the assessment and prediction of bioequivalence is needed. This research should include efforts to develop in vitro tests or animal models that will be valid predictors of bioavailability in man.

The Commissioner recognizes that the January 5, 1973 proposal attempted to set forth general requirements not only for determining the bioavailability of a single drug product but also for determining the comparable bioavailability (i.e., bioequivalence) of two or more drug products. He is now of the opinion that consideration of distinctly different issues (i.e., bioavailability and bioequivalence) under the broad general heading of "bioavailability problems" will cause unnecessary confusion and controversy, if continued in the future. Therefore two separate regulations are now being proposed, § 320.2 relating to bioavailability and § 320.3 relating to bioequivalence. Because these regulations have been changed substantially from the January 5, 1973 proposal, both are being offered at the present time as new proposals for comment.

The Commissioner is of the opinion that the term "bioavailability" should be defined as the rate and extent to which the therapeutic moiety is absorbed and becomes available to the site of drug action usually as estimated by its concentrations in body fluids, rate of excretion, or acute pharmacological effect. A determination of the bioavailability of any drug product requires in vivo testing. The Commissioner agrees with the conclusion of the OTA Drug Bioequivalence Study Panel that most of the analytical methodology and experimental procedures for the conduct of bioavailability studies in man are available, except that additional work may be required to develop means of applying them to certain drug products and special situations of drug use. Elsewhere in this issue of the FEDERAL REGISTER, the Commissioner is proposing regulations defining the term bioavailability, defining the purposes of bioavailability studies, establishing methods and procedures for in vivo testing to determine the bioavailability of drug products, and requiring specific bioavailability data in new drug applications and in supplements to approved new drug applications. If the supplement concerns a significant change in product formulation and in vitro tests are not sufficient to assure the bioavailability of the reformulated product.

The Commissioner also is of the opinion that the procedures set forth in the January 5, 1973 proposal for identifying drug products which need data to show that they are comparable in bioavailability to other drug products which are intended to be used interchangeably, and the methods for determining such bioequivalence, need to be revised and proposed as a separate regulation. Therefore, the Commissioner now pro-

poses regulations to define certain terms relating to bioequivalence, set forth criteria to be used to identify specific drug products for which a bioequivalence requirement should be established, and set forth procedures which the Food and Drug Administration will follow in establishing a bioequivalence requirement for specific drug products or classes of drug products.

The Commissioner proposes to define certain terms as follows:

1. "Drug product" means a finished dosage form (e.g., tablet, capsule, solution, etc. that contains the active drug ingredient generally, but not necessarily, in association with inactive ingredients.

2. "Pharmaceutical equivalents" means 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. Examples of pharmaceutical equivalents are two different brands of tetracycline hydrochloride capsules, each containing 250 mg of tetracycline hydrochloride.

3. "Pharmaceutical alternatives" means drug products that contain the identical therapeutic moiety (or its precursor), but not necessarily in the same amount or dosage form, or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. Examples of pharmaceutical alternatives are tetracycline hydrochloride capsules and tetracycline phosphate capsules, the latter containing an amount of tetracycline equivalent to that in 250 milligrams of tetracycline hydrochloride.

4. "Bioequivalent drug products" means pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a statistically significant difference when administered at the same molar dose of the therapeutic moiety under similar experimental conditions (either single dose or multiple dose). Some pharmaceutical equivalents or pharmaceutical alternatives may be equivalent in the extent of their absorption but not in their rate of absorption and yet may be considered bioequivalent because such differences in rates of absorption may be considered medically insignificant for the particular drug products studied.

5. "Bioequivalence requirement" means a requirement, imposed by the Food and Drug Administration for in vitro and/or in vivo testing of specific drug products, which will be required of all manufacturers as a condition of marketing. The requirement consists of the following:

a. A current in vitro test (usually a dissolution rate test) not correlated with in vivo data, by a method specified by the Food and Drug Administration, in which the drug product is compared with a reference material, or

b. An in vitro bioequivalence standard which has been correlated with in vivo data on bioavailability, and

c. Where so specified, an in vivo bioavailability test. Such in vivo bioavailability testing will ordinarily be required whenever methodology is available to conduct the study by the most sensitive approaches available and there is documented evidence that the particular drug has a strong potential for lacking bioavailability or is a so-called "critical dose" drug or is necessary for the treatment or prevention of a serious disease or condition. The reference material will be a similar dosage form which is the subject of an approved new drug application or another material specified by the Food and Drug Administration (e.g., the active ingredient in solution or suspension).

The Commissioner proposes procedures to deal with bioequivalence problems that arise when pharmaceutical equivalents or pharmaceutical alternatives, administered at the same molar dose of the same therapeutic moiety and intended to be used interchangeably for the same therapeutic effect are not, or may not be, bioequivalent drug products. Such a problem implies that the existing in vitro standards for the drug are not adequate to assure that the products meeting these standards are bioequivalent and/or the drug is not appropriately labeled to reflect its bioavailability characteristics. There are specific drug products (i.e., pharmaceutical alternatives) that meet all applicable in vitro standards, are labeled to be used interchangeably at the same molar dose, and for which the Food and Drug Administration has evidence of lack of bioequivalence when comparison is made to an appropriate reference material. Such differences suggest the need for specific dosage recommendations and/or differences in medical use. Further examination of each specific example may reveal that the in vitro standards are appropriate to optimize the absorption of the therapeutic moiety, but that the drug's labeling may be misleading to the medical profession in that it does not appropriately reflect the pharmacokinetic properties of the drug. The solution in such cases is to require in vivo bioavailability studies only if needed to determine the degree of drug absorption and to relabel the drug whenever medically feasible (i.e., whenever the label can be reasonably understood and not be misleading) to reflect its pharmacokinetic characteristics.

The Commissioner is of the opinion that efforts should be made to develop in vitro tests that will be valid predictors of bioequivalence. He believes that the solution to a bioequivalence problem is to develop an in vitro bioequivalence standard and/or alter the labeling when medically appropriate and feasible. An in vitro bioequivalence standard will as-

sure not only the bioequivalence of different drug products but also batch-to-batch uniformity of the same drug product. However, where an in vitro bioequivalence standard does not exist, an interim solution is, where practicable, (1) in vitro testing alone using a current method specified by the Food and Drug Administration and/or (2) a requirement for in vivo bioavailability testing. This interim requirement should be imposed only until an in vitro bioequivalence standard is available.

The Commissioner recognizes that a few bioequivalence problems have been noted in the past and others may become apparent in the future. However, he believes that relatively few of the currently marketed drug products meeting current in vitro standards and current good manufacturing practices will be found to have medically significant bioequivalence problems. For this reason, he does not believe that it is necessary or in the public interest to undertake the task of developing new in vitro bioequivalence standards for all drug products. The procedures being proposed by the Commissioner are intended to identify bioequivalence problems involving currently marketed drug products and to develop adequate in vitro bioequivalence standards for these drug products.

The Commissioner is of the opinion that it is neither necessary nor feasible to require in vivo bioavailability testing of all drug products which were evaluated as effective under the drug efficacy study. For many such drug products, such testing would involve human risk and would be a waste of human resources with little benefit to the public health. Furthermore, the Commissioner is of the opinion that, for many drug products, the use of a current in vitro test comparing the drug product to a reference material may be adequate to assure the quality and uniformity of drug products which are intended to be used interchangeably as well as all batches of the same drug product.

The procedures in proposed § 320.3 establish a mechanism for determining that a bioequivalence problem exists that requires the imposition of (1) a current in vitro test and, in some cases, a requirement for in vivo bioavailability testing or (2) an in vitro bioequivalence standard. The proposed regulation also provides for amendment of the requirement for in vivo bioavailability testing and/or in vitro testing using a current test specified by the Food and Drug Administration when an in vitro bioequivalence standard is established.

Section 320.3 sets forth the factors, among others, which will be considered by the Commissioner in determining whether a bioequivalence requirement should be established for pharmaceutical equivalents or pharmaceutical alternatives that are labeled to be administered at the same molar dose of the same therapeutic moiety and are intended to be used interchangeably for the same therapeutic effect. These factors are as follows:

1. Evidence from well-controlled clinical trials or controlled observations in

of the finished dosage form, regardless of whether they undergo chemical change or are removed in the process. Each substance should be identified by its established name, if any, or complete chemical name, using structural formulas when necessary for specific identification. If any proprietary preparation is used as a component, the proprietary name should be followed by a complete quantitative statement of composition. Reasonable alternatives for any listed substance may be specified.

7. A full statement of the composition of the drug. The statement shall set forth the name and amount of each ingredient, whether active or not, contained in a stated quantity of the drug in the form in which it is to be distributed (for example, amount per tablet or per milliliter) and a batch formula representative of that to be employed for the manufacture of the finished dosage form. All components should be included in the batch formula regardless of whether they appear in the finished product. Any calculated excess of an ingredient over the label declaration should be designated as such and percent excess shown. Reasonable variations may be specified.

8. A full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of the drug. Included in this description should be full information with respect to any new-drug substance and to the new-drug dosage form, as follows, in sufficient detail to permit evaluation of the adequacy of the described methods of manufacture, processing, and packing and the described facilities and controls to determine and preserve the identity, strength, quality, and purity of the drug:

a. A description of the physical facilities including building and equipment used in manufacturing, processing, packaging, labeling, storage, and control operations.

b. A description of the qualifications, including educational background and experience, of the technical and professional personnel who are responsible for assuring that the drug has the safety, identity, strength, quality, and purity it purports or is represented to possess, and a statement of their responsibilities.

c. The methods used in the synthesis, extraction, isolation, or purification of any new-drug substance. When the specifications and controls applied to such substance are inadequate in themselves to determine its identity, strength, quality, and purity, the methods should be described in sufficient detail, including quantities used, times, temperatures, pH, solvents, etc., to determine these characteristics. Alternative methods or variations in methods within reasonable limits that do not affect such characteristics of the substance may be specified.

d. Precautions to assure proper identity, strength, quality, and purity of the raw materials, whether active or not, including the

specifications for acceptance and methods of testing for each lot of raw material.

e. Whether or not each lot of raw materials is given a serial number to identify it and the use made of such numbers in subsequent plant operations.

f. If the applicant does not himself perform all the manufacturing, processing, packaging, labeling, and control operations for any new-drug substance or the new-drug dosage form, his statement identifying each person who will perform any part of such operations and designating the part; and a signed statement from each such person fully describing, directly or by reference, the methods, facilities, and controls in his part of the operation.

g. Method of preparation of the master formula records and individual batch records and manner in which these records are used.

h. The instructions used in the manufacturing, processing, packaging, and labeling of each dosage form of the new drug, including any special precautions observed in the operations.

i. Adequate information with respect to the characteristics of and the test methods employed for the container, closure, or other component parts of the drug package to assure their suitability for the intended use.

j. Number of individuals checking weight or volume of each individual ingredient entering into each batch of the drug.

k. Whether or not the total weight or volume of each batch is determined at any stage of the manufacturing process subsequent to making up a batch according to the formula card and, if so, at what stage and by whom it is done.

l. Precautions to check the actual package yield produced from a batch of the drug with the theoretical yield. This should include a description of the accounting for such items as discards, breakage, etc., and the criteria used in accepting or rejecting batches of drugs in the event of an unexplained discrepancy.

m. Precautions to assure that each lot of the drug is packaged with the proper label and labeling, including provisions for labeling storage and inventory control.

n. The analytical controls used during the various stages of the manufacturing processing, packaging, and labeling of the drug, including a detailed description of the collection of samples and the analytical procedures to which they are subjected. The analytical procedures should be capable of determining the active components within a reasonable degree of accuracy and of assuring the identity of such components. If the article is one that is represented to be sterile, the same information with regard to the manufacturing, processing, packaging, and the collection of samples of the drug should be given for sterility controls. Include the standards used for acceptance of each lot of the finished drug.

(iv) Identify each front cover with the name of the applicant and the name of the drug.

(v) Use separate pages or sets of pages for each numbered heading, Items 1 through 12, of the new-drug application Form FD-356H. Arrange the parts as described under paragraph (e) (1) (vii) and (viii) of this section. Number the pages of the new-drug application and include a table of contents. Each copy should bear the same page numbering, except that copies No. 2 and No. 3 will not include the page numbers used for the individual clinical case reports and copy No. 3 will not include the page numbers used for the forms FD-1639.

(vi) The labeling should be distributed in three copies of the application as follows: Two sets of labeling in copy No. 1, one set in copy No. 2, and one set in copy No. 3; if the labeling is in printed form, the remaining eight sets should be submitted unbound.

(vii) Arrange the separate numbered items of a multivolume application (items 1 through 12 of Form FD-356H) in the following sequence. A new volume should be started for each of the following parts marked with an asterisk, and within each part as many volumes should be used as are needed to limit each volume to not more than 2 inches in thickness:

- Cover letter, if any; signed Form FD-356H; items 1 through 7 of the Form FD-356H.
- Manufacturing and sample information (items 8 and 9).
- Animal, toxicological, microbiological, and in vitro data (item 10).
- List of investigators; clinical information other than individual case reports (items 11 and 12).
- Forms FD-1639, Drug Experience Report, to be included in a separate volume in copy No. 1 and copy No. 2 only; cover of volume to be marked "FD-1639" (item 12d).
- Individual clinical case reports, to be included in copy No. 1 only (item 12).

(viii) Number each volume in the lower right-hand corner. Start with the number 1.1 and continue with 1.2, 1.3, 1.4, etc., as needed, until all volumes have been identified as 1.... Copies No. 1, No. 2, and No. 3 should bear the identical volume numbers, except that the volumes of individual clinical case reports will be omitted from copies No. 2 and No. 3 and the volumes of forms FD-1639 will be omitted from copy No. 3.

(ix) Submit separate applications for each different dosage form of the drug proposed. It is not necessary to repeat in

each application basic information pertinent to all dosage forms if reference is made to the application containing such information. Include in each application information applicable to the specific dosage form; such as labeling, composition, stability data, and method of manufacture.

(x) Forward amendments, supplements, reports, and other correspondence submitted after the original application in these folders and this format if they contain sufficient material.

The front cover of these submissions should be identified with the name of the applicant, the name of the drug, and the NDA number, if known. Number the volumes as described in paragraph (e) (1) (viii) of this section, using for each subsequent submission a higher number to the left of the decimal point; for example, a two-volume amendment submitted after the original application would be numbered 2.1 and 2.2, and if a one-volume supplement is then submitted, it would be 3.1. The next submission might be 4.1, 4.2, through 4.23. Submissions consisting of only a few pages will be added to the latest ____1 volume and need not be forwarded as a new volume number.

(2) An incomplete application, or one that has not been submitted in triplicate, will be retained but not filed as an application provided for in section 505(b) of the act. The applicant will be notified in what respects his application is incomplete.

(f) *Abbreviated new-drug applications.* Such applications shall contain:

(1) Satisfactory information of the kinds described in items 1 (table of contents), 4 (label and all other labeling), 5 (R_x or OTC statement), and 6 (components) of the new-drug application Form FD-356H, and in lieu of full information described under items 7 and 8 (composition and methods, facilities, and controls), brief statements that:

(i) Include the composition of the drug, stating the name and amount of each ingredient whether active or not, contained in a stated quantity of the drug in the form in which it is to be distributed.

(ii) Identify the place where the drug will be manufactured, processed, packaged, and labeled and the name of the supplier of the active ingredient(s).

(iii) Identify any person other than the applicant who performs a part of those operations and designate the part.

components which may undergo chemical change in the manufacture of the drug and be present in the finished drug product in a modified form intended to furnish the specified activity or effect.

(6) The term "inactive ingredient" means any component other than an "active ingredient" present in a drug.

(7) The term "materials approval unit" means any organizational element having the authority and responsibility to approve or reject components, in-process materials, packaging components, and final products.

(8) The term "strength" means:

(i) The concentration of the drug substance (for example, w/w, w/v, or unit dose/volume basis) and/or

(ii) The potency, that is, the therapeutic activity of the drug substance as indicated by appropriate laboratory tests or by adequately developed and controlled clinical data (expressed, for example, in terms of units by reference to a standard).

(Secs. 501, 701, 52 Stat. 1049-1050 as amended, 1055-1056 as amended (21 U.S.C. 351, 371)) [40 FR 14024, Mar. 27, 1975; 40 FR 26508, June 24, 1975, as amended at 41 FR 11011, Mar. 15, 1976]

PART 211—CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS

Subpart A—General Provisions

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- 211.40 Production and control procedures.
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Subpart D—Packaging and Labeling

- 211.80 Packaging and labeling.

Subpart E—Records and Reports

- 211.101 Master production and control records; batch production and control records.
211.110 Distribution records.
211.115 Complaint files.

AUTHORITY: Secs. 501, 701, 52 Stat. 1049-1050 as amended, 1055-1056 as amended (21 U.S.C. 351, 371).

Source: 40 FR 14025, Mar. 27, 1975, unless otherwise noted.

Subpart A—General Provisions

§ 211.1 Finished pharmaceuticals; manufacturing practice.

(a) The criteria in §§ 211.20-211.115, inclusive, shall apply in determining whether the methods used in, or the facilities or controls used for, the manufacture, processing, packing, or holding of a drug conform to or are operated or administered in conformity with current good manufacturing practice to assure that a drug meets the requirements of the act as to safety and has the identity and strength and meets the quality and purity characteristics which it purports or is represented to possess as required by section 501(a)(2)(B) of the act.

(b) The regulations in this part permit the use of precision automatic, mechanical, or electronic equipment in the production and control of drugs when adequate inspection and checking procedures are used to assure proper performance.

§ 211.10 Personnel.

(a) The personnel responsible for directing the manufacture and control of the drug shall be adequate in number and background of education, training, and experience, or combination thereof to assure that the drug has the safety, identity, strength, quality, and purity that it purports to possess. All personnel shall have capabilities commensurate with their assigned functions, a thorough understanding of the manufacturing control operations they perform, the necessary training or experience, and adequate information concerning the reason for application of pertinent provisions of this part to their respective functions.

(b) Any person shown at any time (either by medical examination or supervisory observation) to have an apparent illness or open lesions that may adversely affect the safety or quality of drugs shall be excluded from direct contact with drug products until the condition is corrected. All employees shall be instructed to report to supervisory personnel any conditions that may have such an adverse effect on drug products.

Subpart B—Construction and Maintenance of Facilities and Equipment

§ 211.20 Buildings.

Buildings shall be maintained in clean and orderly manner and shall

drug products to assure the bioequivalence of these products. This testing will be done both in-house and through grants and contracts to competent university scientists and other appropriate investigators.

11. Several comments objected to what they consider to be the inherent assumption in the proposal that no prescription drug products except those listed in the preamble have a bioequivalence problem. The comment stated that FDA has failed to produce any valid scientific evidence to back up this assumption of equivalence.

The Commissioner advises that the proposed regulations were not based on the inherent assumption that only the prescription drug products listed in the preamble have a bioequivalence problem. The proposed regulations under § 320.3 (b) listed factors that the Commissioner would consider in determining whether there is a bioequivalence problem that requires the establishment of a bioequivalence requirement. Using these criteria, the Commissioner made a tentative finding that the drug products listed in the preamble had a known or potential bioequivalence problem. The purpose of the list was to generate public understanding of how FDA intends to apply the factors set forth in proposed § 320.3(b) to identify drug products for which a bioequivalence requirement should be established. Although an attempt was made to identify each drug product with a known or potential bioequivalence problem, the Commissioner recognizes that the list may omit some drug products with a known or potential bioequivalence problem. Likewise, the Commissioner emphasizes that a drug product's inclusion on the list does not necessarily imply that FDA has positive evidence of bioequivalence among the various brands of the drug product.

12. One comment questioned the statement in the preamble to proposed § 320.3 that the Commissioner believes that relatively few of the marketed drug products meeting current in vitro standards and current good manufacturing practices will be found to have medically significant bioequivalence problems. The comment noted that the lengthy list of drug products in the preamble suggests more than a few potential bioequivalence problems.

In paragraph 11, the Commissioner emphasizes that a drug product's inclusion on the list does not necessarily imply that FDA has positive evidence of bioequivalence among the various brands of the drug product. In compiling the list, FDA took a conservative approach. Therefore, a drug product was included on the list if, in FDA's opinion, there was any suspicion that the drug product had a known or potential bioequivalence problem or was a member of a class of drug products for which there was suspicion that at least one member of the class had a known or potential bioequivalence problem. The Commissioner is of the opinion that, as evidence of bioequivalence is closely examined, few of the drug products listed will be determined to have well-documented, medi-

cally significant bioequivalence problems. A "medically significant bioequivalence problem" is one that would result in therapeutic failure or a hazard to a patient if different brands of the same drug product or different batches of the same brand are not bioequivalent. The Commissioner believes that a determination of bioequivalence is most critical in a drug product that has a narrow therapeutic-toxicity dosage range and requires careful patient titration and monitoring for safe and effective use.

13. Two comments objected to the list of drug products included in the preamble and identified as having known or potential bioequivalence problems. The comment added that the list is arbitrary, and, contrary to a statement made in the preamble, does not provide adequate information to manufacturers to assemble data and conduct bioequivalence studies in anticipation of a bioequivalence requirement. Several comments suggested that the list be amended to include additional drug products.

In responding to the comment in paragraph 11 of this preamble, the Commissioner acknowledges that the list of drug products may omit some drug products with a known or potential bioequivalence problem. The Commissioner does not agree that the list is arbitrary. The drug products listed were selected by the Commissioner using the factors proposed in § 320.3(b). The purpose of the list was to alert persons marketing a drug product on the list that, on the basis of an in-house review of data available to FDA, the Commissioner is concerned that the product has a bioequivalence problem and he will likely propose to establish a bioequivalence requirement for the drug product. At the time the Commissioner proposes a bioequivalence requirement, he will document the data to support the requirement. These persons, therefore, can rely on this advance information if they wish to conduct bioequivalence studies in anticipation of the establishment of the requirement by rule making.

The majority of the drug products listed in the preamble and identified as having a known or potential bioequivalence problem were drug products evaluated as effective for at least one indication in the Drug Efficacy Study. The Commissioner advises that FDA will continue to require the submission of bioavailability data in a full or abbreviated NDA for any of these products and for identical, related, or similar drug products. This policy is being codified in § 320.22(c) (21 CFR 320.22(c)) of the bioavailability regulations under Subpart B—Procedures for Determining the Bioavailability of Drug Products published elsewhere in this issue of the FEDERAL REGISTER. The FDA intends to propose in the near future under the procedures set forth in Subpart C of Part 320 the establishment of a bioequivalence requirement for all of these drug products, which upon examination, are determined to have well-documented, medically significant bioequivalence problems. If a bioequivalence requirement is finally established for a drug product after completion of these

procedures, the applicant will be required to submit data in the full or abbreviated NDA to demonstrate that the product meets the bioequivalence requirement.

The Commissioner also advises that FDA's current policy is that, until a bioequivalence requirement is established for a drug product, manufacturers submitting a full or abbreviated NDA for a drug product already identified by FDA as having a known or potential bioequivalence problem will be required to meet the same requirements as previous manufacturers. Thus if previous manufacturers have been required to conduct in vivo studies, new manufacturers will be required to conduct in vivo studies even though there is evidence that a bioequivalence requirement could be established on the basis of an in vitro test. This assures that opportunity for public comment will be provided before an in vitro test is substituted for an existing in vivo test to demonstrate bioequivalence, and that competing firms are treated fairly and equally by the agency. The Commissioner advises that, pursuant to the agency's policy of minimizing human studies, FDA will give priority to the establishment of bioequivalence requirements to those products for which an in vitro test is available.

DEFINITIONS

14. One comment objected to the definition of "drug product" proposed in § 320.1(b). The comment stated the definition should connote an item that is capable of being introduced into interstate commerce and should embrace the active drug ingredient, the labeling, and the final package in which the product is distributed, and not merely the product's dosage form. The comment recommended that "drug product" be defined as "a dosage form defined by the USP monograph in a suitable protective container with labeling that includes directions for use and storage."

The Commissioner does not agree that the term "drug product" should be defined, for the purposes of the bioavailability and bioequivalence regulations, to include the container and labeling. The purpose of defining the term "drug product" is to differentiate that term from the term "drug", i.e., the active drug ingredient. The Commissioner does not believe that the suggested change adds clarity to the definition. On the contrary, he believes that inclusion of the container and labeling in the definition of drug product might mislead persons into believing that a bioequivalence requirement would have to specify the type of container and labeling. The purpose of the bioequivalence regulations is to assure that pharmaceutical equivalents or pharmaceutical alternatives have equivalent bioavailability. The container and labeling have no bearing on this purpose. While a container may affect the stability of a drug product, a product whose strength or purity has deteriorated over time is no longer a pharmaceutical equivalent or a pharmaceutical alternative.

15. One comment concerning the definition of the term "pharmaceutical al-

"How Supplied" section of the Package Insert. In addition to information on the batch number and strength of the drug product used, the source of the active drug substance, and the tests performed in the stability studies, the stability data should provide the following information for each container, closure or stopper:

1. construction material (i.e., composition), and the material's manufacturer and supplier;
 2. complete listing of all fill volumes and container sizes and how many units are contained in each;
 3. closure code number or stopper dimensions, and liner description (if any), and an indication if the closure is described as "child-resistant."
 4. any filler material used as part of the container-closure system tested; and
 5. description of application of torque for oral dosage forms or method of crimp sealing and container integrity testing for parenteral products.
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EFFECTIVE DATE

This guide is effective upon date of publication.

NOTE

¹21 CFR 314.50(d)(1)(ii) requires an application to contain stability data with the proposed expiration date. 21 CFR 314.55 extends this requirement to an ANDA. See also, Sec. 314.94(a)(9), Abbreviated New Drug Application Regulations; Proposed Rule dated July 10, 1989 (54 FR at 28923) and "Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics," February 1987, pp. 5, 9, and 10.

8. Product Fee Triggers

If the other product fee criteria are met, an original application or supplement with or without clinical data pending after September 1, 1992 would trigger product fees for all prescription drugs listed under section 510.

9. Different strengths or potencies

Products that differ in strength or potency are subject to separate product fees. Products of the same strength or potency packaged in different container sizes are not subject to separate fees. The primary determining criterion is strength or potency, which is identified by the product field, the middle segment of the National Drug Code (NDC). However, where distinct differences exist between products of the same potency (e.g., Tuberculin Purified Protein Derivative (PPD), Tine Test versus Tuberculin PPD for intradermal injection, or oral contraceptives products in 21 and 28 day regimens), FDA will also consider the product portion of the NDC. In such cases, if the product codes are different, normally a separate fee will be assessed for each product.

10. DESI Products

Products that are currently undergoing DESI review but have not yet been found to be effective do not qualify for user fees. The standard for approval of new drugs established in the 1962 amendments to the FD&C Act requires demonstration of both safety and effectiveness. Approvals for such products prior to 1962 were on the basis of safety only. Therefore, they are not considered to be prescription drug products approved under section 505(b)(1) until their review under DESI is completed.

11. Large Volume Parenterals (LVP's)

LVP's approved before September 1, 1992, are not subject to product fees. Parenteral products sold in powders for reconstitution do not qualify for the exclusion for LVP's and are subject to fees. The legislative history (Senate Joint Statement) defines LVP's as "single dose sterile fluids." Products used for irrigation can be considered LVP's under the Act.

12. Prescription Products Composed Wholly or Partly of Insulin: "Human drug application" is defined in the PDUFA as an application for approval of a new drug submitted under section 505(b)(1) and certain applications submitted under