U.S. Pharmacopeia
The Standard of Quality℠

December 10, 1999

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

Re: "Guidance for Industry: Chemistry, Manufacturing and Control Changes to an Approved NADA or ANADA"
Docket No. 99D-165 1

Dear Sir or Madam:

This letter provides the comments of the United States Pharmacopeia (USP) on the proposed guidance for industry on changes to an approved new animal drug application (NADA) or abbreviated new animal drug application (ANADA). Notification of this guidance document appeared in the October 1, 1999 Federal Register.[1] This guidance accompanies proposed regulations issued by the Food and Drug Administration (FDA) on "Supplements and Other Changes to Approved New Animal Drug Applications."[2] USP's comments to this proposed regulation are attached and incorporated into these comments by reference.[3]

USP believes that the guidance must be made consistent with the regulatory scheme set forth in the Federal Food, Drug, & Cosmetic Act (FD&C Act) and with the recently issued guidance by FDA's Center for Drug Evaluation and Research (CDER) on supplements to new drug applications (NDA) and abbreviated new drug applications (ANDA).[4] To do so, USP suggests that the Center for Veterinary Medicine (CVM) amend its guidance to permit manufacturers of animal drugs to file an annual report for those changes in specifications and in labeling made to comply with an official compendium.

According to section 50 1 (b) of the FD&C Act, a drug, including those for use in animals, is considered adulterated if it fails to comply with the standards of an official compendium.' If a drug differs from the official standards of strength, quality, or purity, section 501 (b) provides that the difference shall be plainly stated on the

[1] 64 Fed. Reg. 53393 (Oct. 1, 1999).
[2] Id. at 53281.
[3] Attachment 1.
[4] "Guidance for Industry: Changes to an Approved NDA or ANDA" (hereinafter "Changes to an Approved NDA or ANDA") FDA, CDER (November 1999); Attachment 2.
[5] 21 U.S.C. § 351(b). A drug is defined as " (A) articles recognized in the official United States Pharmacopeia, official Homeopathic Pharmacopeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any articles specified in clause (A), (B) or (C). Id. § 321(g)(1)(emphasis added).

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product's label. Such determinations are to be made in accordance with the analytical procedures set forth in the official compendium.

The proposed regulations and the corresponding guidance require that major and moderate changes in specifications (i.e., tests, analytical procedures, and acceptance criteria) be submitted to FDA in a supplemental application.[6] According to the guidance, minor changes in specifications may be submitted in an annual report, including "[a]ny change made to comply with an official compendium that is consistent with FDA requirements and that provides the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application."[7]

However, what meets this type of minor change is unclear. Rather than guess how FDA will interpret "FDA requirements" and "increased assurance," manufacturers are likely to submit a supplemental application for such changes. As a result, manufacturers will refrain from making changes to comply with an official compendium before FDA review or approval of the supplemental application. Such action could result in legal difficulties since products that are not modified to comply with a change in a *USP-NF* standard may be considered adulterated unless the difference is plainly stated on its label. The product also may be considered adulterated under state Food and Drug laws or under Pharmacy Acts, many of which have adopted the adulteration provisions in the FD&C Act.

In addition, since sponsors and USP are unlikely to know about these "FDA requirements" in advance, there would be no consistent regulatory method. As a result, other governmental bodies (Federal and State) and purchasers could not rely on published compendia1 methods as being the regulatory method for a particular drug product, a result contrary to Congressional intent as expressed in section 501(b) of the FD&C Act.

Such a result also appears inconsistent with the agency's intent, as expressed in a recent letter, to support USP standards. In this letter, Dr. Bernard Schwetz, FDA's Acting Deputy Commissioner of Food and Drugs, stated that FDA intends "to help protect USP standards recognition from erosion through changes in regulatory policy, where appropriate."[8] Such support would be clearly appropriate in CVM's guidance, which should reflect the statutory requirement that manufacturers comply with official compendia1 standards.

If the agency is suggesting in the guidance that the compendia1 tests or methods of assay are insufficient, FDA should follow the appropriate statutory procedure in section 50 1 (b) to modify them.[9] According to section 501(b), FDA must bring information on "insufficient" tests or methods to the attention of the compendia1 body, e.g., the USP. If the compendia1 body fails to provide sufficient tests or methods of

[6] 64 Fed. Reg. at 53291-93; FDA, Center for Veterinary Medicine, "Draft Guidance for Industry: Chemistry, Manufacturing and Control Changes to an Approved NADA or ANADA" 17-20 (June 1999).
[7] Id. at 20.
[8] Letter from Bernard Schwetz, D.V.M., Ph.D., FDA Acting Deputy Commissioner of Food and Drugs, to Arline Bilbo, USP Member Services Manager, 2 (November 1, 1999); Attachment 3.
[9] 21 U.S.C. § 351(b).

assay, only then should FDA promulgate regulations for tests or methods of assay. Under the proposed guidance, FDA could disapprove or fail to approve the NADA or ANADA supplement containing the changed compendia1 method, instead of notifying USP of any insufficiencies and providing USP with an opportunity to revise the current tests or develop new tests or methods of assay. This would result in inconsistent regulatory methods for the same drug and would cause confusion within the industry.

The difference between the NADA, ANADA and compendia1 specifications, tests or methods of assay can create a regulatory quagmire for FDA. For example will the agency be able to take legal action against a product failing a USP requirement, if the agency is responsible for the different specification or analytical procedure? Conversely will the FDA be able to hold a manufacturer to the NADA specification, when the statute indicates the USP standard or method of analysis is the one to be used? This would result in a difficult position for FDA.

The guidance also fails to mention labeling changes made to comply with an official compendium. Section 502(g) of the FD&C Act provides that a drug shall be deemed misbranded unless it is labeled and packaged as prescribed in an official compendium.[10] Other sections of the FD&C Act require labeling dependent upon the compendium. For example, the FD&C Act requires the drug label to bear a . - nonproprietary (i.e. generic) name, which is defined in section 502(e)(3) as the. FDA established name or the official title in an official compendium.[11] For the most part, FDA has relied upon USP to determine the official names for a drug. Manufacturers seeking to change labeling to comply with an official compendium would be required to submit a supplemental application, prior to making any such change, rendering their products misbranded under the FD&C Act.

USP revisions can result in hundreds of specification and labeling changes within any given year. Since the proposed guidance would require submission of supplemental applications for some of these changes, manufacturers would be in the difficult position of marketing a product that may be considered adulterated or misbranded, until the proper submission or approval of the supplement.

USP encourages the agency to follow its recently issued guidance "Changes to an Approved NDA or ANDA." In that guidance, the agency permits a manufacturer making a change in specifications or in labeling to comply with an official compendium to submit the information in the annual report.[12] The guidance recognizes the procedures successfully implemented by FDA and USP for full review of compendia1 revisions, including: (1) USP's Document Disclosure Policy; (2) public notice and comment revisions in USP's *Pharmacopeial Forum,* and the attendant Discussion Open House opportunities; (3) *USP-NF* Supplement Open House; (4) the FDA-USP ad hoc reviewers program; (5) the Compendia1 Operations Branch; (7) liaisons to USP assigned by FDA Centers; (8) FDA review of changes in annual reports responding to compendia1 changes; and (9) high level meetings.

[10] Id. § 352(g). FDA may modify the method of packing.
[11] Id. §§ 352(e)(l)(A)(i) and 352(e)(3).
[12] "Changes to an Approved NDA or ANDA" at 19, 25.

USP specifically requests that CVM's draft guidance be modified as follows:

- On page 20, at the end of line 567, delete all text after the words "official compendium." The statement would then read:

    1. Any change made to comply with an official compendium.

- On page 26, after line 752, add the following sentence;

    5. Any change made in labeling to comply with an official compendium.

We believe that these changes are consistent with the regulatory scheme provided by the FD&C Act and with CDER's November 1999 guidance on "Changes to an Approved NDA or ANDA."

You may contact me at (301) 816-8256 if you have any questions about these comments. Thank you for your careful consideration.

Sincerely,

Joseph G. Valentino
Senior Vice President and General Counsel

Attachments

cc: Stephen F. Sundlof, D.V.M., Ph.D.
Director, Center for Veterinary Medicine

Yana R. Mille, R.Ph.
Chief, Compendial Operations Branch, FDA

Jerome A. Malperin
Executive Vice President, USP

Attachment 1

U.S. Pharmacopeia
The Standard of Quality℠

December 1, 1999

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

Re: "Supplements and Other Changes to Approved New Animal Drug Applications"
Docket No. 99N-1415

Dear Sir or Madam:

This letter provides the comments of the United States Pharmacopeia (USP) to the Food and Drug Administration's (FDA) proposed rule on "Supplements and Other Changes to Approved New Animal Drug Applications (NADA)."[1]

USP, established in 1820, is a not-for-profit organization that develops and disseminates legally recognized standards of strength, quality, purity, packaging and labeling for drugs. The standards are published in the *United States Pharmacopeia-National Formulary (USP-NF)*. These texts are legally recognized as official compendia, and the compendia1 standards have been enforceable since 1906.[2] The Federal Food, Drug, and Cosmetic Act (FD&C Act) requires drugs, which include those for animal use, to be in compliance with USP compendia1 standards.[3] These provisions are not superseded by, but instead work in conjunction with, the statutory requirements on New Drug and New Animal Drug approvals.[4]

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[1] *64* Fed. Reg. 53281 (Oct. 1, 1999).

[2] The standards are enforceable under the Federal Food, Drug, and Cosmetic Act; see 21 U.S.C. §§ 321(g)(l)(A), 35 I(b) and 352(g). Congress specifically recognized as official the changes to the *USP-NF* that appear in the supplements by defining official compendium as "the official United States Pharmacopeia, official Homeopathic Pharmacopeia of the United States, official National Formulary, or any supplement to any of them." Id. § 321(j) (emphasis added).

[3] The definition of drug includes " (A) articles recognized in the official United States Pharmacopeia, official Homeopathic Pharmacopeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any articles specified in clause (A), (B) or (C). Id. § 321(g)(1)(emphasis added).

[4] According to 21 U.S.C. § 351(b), a drug is adulterated

> [i]f it purports to be or is represented as a drug the name of which is recognized in an official compendium, and its strength differs from, or its quality or purity falls below, the standards set forth in such compendium. Such determination as to strength, quality, or purity shall be made in accordance with the tests or methods of assay set forth in such compendium, except that whenever tests or methods of assay have not been prescribed in such compendium, or such tests or methods of assay as are prescribed are, in the judgment of the Secretary, insufficient for the making of such determination, the Secretary shall bring such fact to the attention of the

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The regulations proposed by the FDA's Center for Veterinary Medicine (CVM) appear consistent with those proposed by the agency's Center for Drug Evaluation and Research (CDER) for "Supplements and Other Changes to an Approved Application."[5] USP submitted comments to CDER's proposed regulation, a copy of which is enclosed and incorporated by reference into these comments.[6]

USP opposes adoption of CVM's proposed regulations because they: (1) are inconsistent with the statutory and regulatory scheme that recognize compendia1 standards to assure the quality of drugs in the marketplace; (2) would require supplements for labeling changes made to comply with compendia1 revisions, which would cause confusion and uncertainty about a product's legal status; and (3) would impose unnecessary, burdensome requirements on industry.

USP urges the agency to amend the proposed regulations to provide a regulatory exemption consistent with that recommended by USP for CDER's proposed regulations, 2 1 C.F.R. § 3 14.70. This exemption would permit manufacturers of animal drugs to make changes in specifications and in labeling to comply with an official compendium without tiling a supplemental application, provided these changes are submitted in the annual report.

This exemption also would be consistent with that recognized by CDER in its recently issued final guidance on supplements to new drug applications (NDA) and abbreviated new drug applications (ANDA) permitting changes in specifications and in labeling made to comply with an official compendium, provided the changes are

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> appropriate body charged with the revision of such compendium, and if such body fails within a reasonable time to prescribe tests or methods of assay which, in the judgment of the Secretary, are sufficient for purposes of this paragraph, then the Secretary shall promulgate regulations prescribing appropriate tests or methods of assay in accordance with which such determination as to strength, quality, or purity shall be made. No drug defined in an official compendium shall be deemed to be adulterated under this paragraph because it differs from the standard of strength, quality, or purity therefor set forth in such compendium, if its difference in strength, quality, or purity from such standards is plainly stated on its label. Whenever a drug is recognized in both the United States Pharmacopeia and the Homeopathic Pharmacopeia of the United States it shall be subject to the requirements of the United States Pharmacopeia unless it is labeled and offered for sale as a homeopathic drug, in which case it shall be subject to the provisions of the Homeopathic Pharmacopeia of the United States and not to those of the United States Pharmacopeia .

As provided by 21 U.S.C. § 352(g), a drug is misbranded

> [i]f it purports to be a drug the name of which is recognized in an official compendium, unless it is packaged and labeled as prescribed therein. The method of packing may be modified with the consent of the Secretary. Whenever a drug is recognized in both the United States Pharmacopeia and the Homeopathic Pharmacopeia of the United States, it shall be subject to the requirements of the United States Pharmacopeia with respect to packaging, and labeling unless it is labeled and offered for sale as a homeopathic drug, in which case it shall be subject to the provisions of the Homeopathic Pharmacopeia of the United States, and not to those of the United States Pharmacopeia, except that in the event of inconsistency between the requirements of this paragraph and those of paragraph (e) as to the name by which the drug or its ingredients shall be designated, the requirements of paragraph (e) shall prevail.

[5] 64 Fed. Reg. 34608 (June 28, 1999).

[6] Attachment 1.

submitted in the manufacturer's annual report.[7] In addition, the exemption would be consistent with the requirements under the FD&C Act that recognize compendial standards, methods of analysis, and labeling requirements and would eliminate a redundant review by FDA, without compromising the safety and efficacy of animal drugs.

1. FDA's Proposed Regulations Are Inconsistent With The Statutory Structure For Drug Approval And Quality

The proposed regulations undermine the current statutory scheme that recognizes the standards for drug strength, quality, and purity provided by the *USP - NF*. Section 501(b) of the FD&C Act sets standards for product quality by defining adulterated drugs as those that have their strength, quality or purity falling below compendia1 standards.[8] Section 501(b) also requires that adulteration be determined by compendia1 tests or methods of assay.

The proposed regulations ignore section 50 1 (b) by imposing additional requirements even on minor changes made to comply with an official compendium. Specifically, the proposed regulations state that these changes must be "consistent with FDA requirements" and must provide "increased assurance that the new animal drug will have the characteristics of identity, strength, quality, purity, or potency that it purports or is represented to possess."[9] Section 50 1 (b) requires compliance with all compendia1 standards, not only those consistent with FDA requirements and those that provide increased assurances. Moreover, the meaning of these phrases is so vague that it will likely cause confusion in the industry and perhaps within the agency.

Not only are the phrases "FDA requirements" and "increased assurance" unclear, but if they refer to those methods and specifications in approved NADAs, they are likely to be confidential and unknown to USP. Therefore, these requirements would seem to undermine the clear intent of the statute to recognize public, compendia1 standards that are readily available to the entire pharmaceutical industry, health care professions, and the public.

Addition of these proposed regulatory requirements also appears to suggest that compendial methods of analysis are insufficient. The appropriate mechanism to remedy insufficiencies is provided by section 501(b) of the FD&C Act. According to the statute, FDA must bring information on insufficient tests or methods to the attention of the compendia1 body. If the compendial body fails to provide sufficient tests or methods of assay, only then would FDA have the authority to promulgate regulations for tests or methods of assay. FDA has never had to take corrective action under section 501(b) due to insufficiencies in the compendia1 procedures related to specifications. If such insufficiencies exist, FDA has failed to address the alternative remedies available to it that are relevant to such matters.

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[7] "Guidance for Industry: Changes to an Approved NDA or ANDA" FDA, CDER 19, 25 (November 1999); Attachment 2.

[8] 21 U.S.C. $351(b).

[9] 64 Fed. Reg. at 53293 (to be codified at 21 C.F.R. § 514.8(b)(4)(ii)(A)).

FDA's proposed regulations also are inconsistent with the statutory requirement that FDA cooperate with scientific societies in the revision of the *USP* and in the development of methods of analysis and mechanical and physical tests necessary to carry out the work of FDA. [10] Instead of eliciting cooperation, it appears that FDA is unilaterally imposing its own vague standards, which violate the spirit of the law. In a recent letter from Dr. Bernard Schwetz, FDA's Acting Deputy Commissioner of Food and Drugs, FDA articulated its support "to help protect USP standards recognition from erosion through changes in regulatory policy, where appropriate."* [11] Such support would be clearly appropriate in these FDA proposed regulations, which should reflect the statutory requirement that manufacturers comply with official compendia1 standards.

2. The Proposed Regulations Requiring Supplements For Labeling Changes Consistent With Compendia1 Revisions Would Likely Cause Confusion And Uncertainty About A Product's Legal Status

The proposed regulations also undermine the statutory scheme recognizing consistency in labeling of drug products. According to § 502(g) of the FD&C Act, a drug is misbranded if it is a drug recognized in an official compendium and is not labeled and packaged as described in the compendium." In addition, § 502(e)(l)(A)(i) of the FD&C Act requires a drug to bear a nonproprietary (i.e. generic) name. [13] This is defined in section 502(e)(3) as the FDA established name or the official title in an official compendium. [14] For the most part, FDA has relied upon USP to determine the official names for a drug. Drug names often change as the nature of products change.

CVM's proposed regulations do not specifically mention the procedure for supplemental applications for labeling changes made to comply with an official compendium. However, the regulations appear to require a manufacturer making labeling changes consistent with compendia1 changes to submit a supplement for approval prior to distributing the product. [15] Specifically, proposed 21 C.F.R. § 514.8(c)(2)(D) describes the labeling changes requiring the submission and approval of a supplement prior to product distribution, which include "any other changes in labeling except ones described in paragraph (c)(3)." [16] Proposed 21 C.F.R. § 5 14.8(c)(3), which permits labeling changes to be placed into effect before approval of a supplemental application, does not include labeling changes made to comply with those of *USP-NF*. [17]

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[10] 21 U.S.C. § 377. This states that "[t]he Secretary, in carrying into effect the provisions of this chapter, is authorized on and after July 12, 1943, to cooperate with associations and scientific societies in the revision of the United States Pharmacopoeia and in the development of methods of analysis and mechanical and physical tests necessary to carry out the work of the Food and Drug Administration."

[11] Letter from Bernard Schwetz, D.V.M., Ph.D., FDA Acting Deputy Commissioner of Food and Drugs, to Arline Bilbo, USP Member Services Manager, 2 (November 1, 1999); Attachment 3.

[12] 21 U.S.C. § 352(g); see supra note 4.

[13] Id. § 352(e)(l)(A)(i).

[14] Id. § 352(e)(3).

[15] 64 Fed. Reg. at 53293-94 (to be codified at 21 C.F.R. § 514.8(c)(1), (2), and (3)).

[16] Id. at 53293.

[17] Id. at 53293-94.

If USP makes official a change to a labeling requirement and a company cannot comply until FDA approves the change, the marketed drug, in the intervening period, technically may be misbranded or adulterated if it fails to meet the changed compendial requirements. There is likely to be confusion in the marketplace and more opportunity for errors if manufacturers individually must seek approval to change their labeling and the labels do not change uniformly.

It is clear that public standards, including labeling for drugs, is in the public interest because the standards serve to uniformly assure the quality of drugs in the marketplace. Changes in the standards and in labeling to comply with compendia1 changes should be made simultaneously for all brands of the same drug to assure consistency in the marketplace. Implementing changes at various times for different brands of the same drug based on each manufacturer's interpretation of the nature of the change, may cause inconsistencies in drug quality.

3. The Proposed Regulations Would Impose Unnecessary, Burdensome Requirements On Industry

USP believes that the implementation of the proposed regulations will impose on industry substantial paperwork burdens that are unnecessary under the statute. Under the proposed regulations, manufacturers of animal drug products must file and obtain FDA approval of supplemental applications for labeling changes made to comply with an official compendium, although the FD&C Act requires immediate compliance with such changes, without supplemental applications and FDA review. In addition, manufacturers are likely to file supplemental applications and obtain approval for any change made to comply with an official compendium to ensure compliance with the proposed, vague requirement that such change be "consistent with FDA requirements and provide[ ] increased assurance that the new animal drug will have the characteristics of identity, strength, quality, purity, or potency that it purports or is represented to possess."[18]

If USP changes the compendia1 requirements to delete a test for a commonly used excipient (such as magnesium stearate, an excipient commonly found in tablet formulations) or if USP changes a general method of analysis, the proposed regulations may result in manufacturers filing supplements for every NADA and ANADA using that excipient or general analytical method.[19] Similarly, any change in compendia1 would result in supplemental applications for every NADA and Abbreviated New Animal Drug Application (ANADA). The number of supplements generated by such changes could prove overwhelming for both industry and CVM.

It is unclear what justification exists for these unnecessary regulatory burdens on companies and for the added review time on the agency. FDA has not provided a reason to impose these filing requirements. FDA has not provided USP with evidence that changes made to comply with compendia1 standards or labeling have resulted in

[18] Id. at 53293.

[19] Since 1995, almost 4,000 individual revisions to the *USP-NF* were made official. In addition, eight new chapters establishing general requirements were published. These new requirements have necessitated hundreds of other changes.

drugs that are unsafe, not effective, or of poor quality. Nor has the agency provided any public policy concerns that would justify imposing the filing requirements for these changes. It appears that the proposed regulations would impose unnecessary costs for industry, the agency, and ultimately consumers, without providing any clear benefit.

FDA already has the opportunity to review USP compendia1 changes and to provide comments through the agency's Compendia1 Operations Branch located in CDER. Under its current policies, USP publishes all proposed changes in compendia1 standards in the *Pharmacopeial Forum,* a bimonthly publication providing an opportunity for public review of and comment on revisions affecting the *USP-NF.* There is no need for a redundant review by the agency of supplemental applications containing these changes.

Nor are these proposed regulations consistent with the intent of the Food and Drug Administration Modernization Act (FDAMA), which was enacted, in part, to improve drug regulation and to expedite the availability of drug products to consumers. Section 116 of FDAMA requires the submission and approval of a supplemental application for major manufacturing changes but allows FDA to exempt certain changes in specifications.[20] FDAMA therefore would support a system that provides an exemption from filing a supplemental application for any change made to comply with an official compendium. Such a system would achieve the goal of safe, high quality products in the marketplace and would be more efficient and less costly than the proposed regulations.

Conclusion

USP requests that the agency amend its proposed regulations to permit a manufacturer that makes any change to a specification or labeling to comply with a change in an official compendium to provide information on the change in the annual report (minor changes and stability report). Specifically, USP proposes the following amended language to the proposed regulation:

21 C.F.R. § 514.8

. . .

(b) *Manufacturing changes to an approved application*

. . .

[20] The Food and Drug Administration Modernization Act of 1997 § 116, Pub. L. No. 105-l 15, (codified at 21 U.S.C. § 356a (1997)). FDA has the authority to exempt certain changes from the definition of major manufacturing changes. Major manufacturing change are those that have "substantial potential to adversely affect the identity, strength, quality, purity, or potency of the drug as they may relate to the safety or effectiveness of a drug" including: (A) a change in the qualitative or quantitative formulation of the drug involved or in the specifications in the approved application or license, unless exempted by regulation or guidance; (B) a change determined by FDA to require completion of an appropriate clinical study demonstrating equivalence of the drug to the drug manufactured without the change; or (C) another type of change determined by FDA to have substantial potential to adversely affect the safety or effectiveness of a drug. 21 U.S.C. § 356a (c)(2)(emphasis added).

(4) Changes and updated stability data to be described and submitted in an annual report (minor changes).

. . .

(ii) These changes include but are not limited to:

(A) Any change made to comply with an official compendium; ~~that is consistent with FDA requirements and provides increased assurance that the new animal drug will have the characteristics of identity, strength, quality, purity, or potency that it purports or is represented to possess;~~

. . .

(c) Labeling and other changes to an approved application-

(I) General Provisions. The applicant must notify FDA about each change in each condition established in an approved application beyond the variations already provided for in the application. The notice is required to describe the change fully. **Any change made in labeling to comply with an official compendium may be submitted in the annual report.**[21]

. . .

* * * * *

These amendments are consistent with: (1) the current regulatory scheme that recognizes and utilizes official compendial requirements; (2) the participation by the agency in the public review process in developing and monitoring compendial requirements; (3) the changes made in CDER's final guidance on "Changes to an Approved NDA or ANDA;" and (4) USP's comments to CDER's proposed regulation on supplemental applications.

You may contact me at (301) 8 16-8256 if you have any questions about these comments. Thank you for your careful consideration.

Sincerely,

Joseph G. Valentino
Senior Vice President and General Counsel

Attachments

cc: Bernard Schwetz, D.V.M., Ph.D.
Acting Deputy Commissioner of Food and Drugs

Stephen F. Sundlof, D.V.M., Ph.D.
Director, Center for Veterinary Medicine

[21] The language added by USP appears in bold. USP has indicated the language to be removed in the proposed regulations by striking through it.

Yana R. Mille, R.Ph.
Chief, Compendial Operations Branch, FDA

Jerome A. Halperin
Executive Vice President, USP

Jordan L. Cohen, Ph.D.
Chairman, USP Board of Trustees

Dennis K. J. Gorecki, Ph.D.
Chairman, USP Division of Standards Development Executive Committee

Attachment 2

Guidance for Industry

Changes to an Approved NDA or ANDA

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
November 1999
CMC

Guidance for Industry

Changes to an Approved NDA or ANDA

Additional copies are available from:

Drug Information Branch (HFD-210)
Center for Drug Evaluation and Research (CDER)
5600 Fishers Lane, Rockville, MD 20857 (Tel) 301-827-4573
Internet at http://www.fda.gov/cder/guidance/index.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
November 1999
CMC

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GUIDANCE FOR INDUSTRY[1]

Changes to an Approved NDA or ANDA

I. INTRODUCTION

On November 21, 1997, the President signed the Food and Drug Administration Modernization Act (the Modernization Act).[2] Section 116 of the Modernization Act amended the Food, Drug, and Cosmetic Act (the Act) by adding section 506A (21 U.S.C. 356a), which provides requirements for making and reporting manufacturing changes to an approved application and for distributing a drug product made with such changes.

The purpose of this guidance is to provide recommendations to holders of new drug applications (NDAs) and abbreviated new drug applications (ANDAs) who intend to make postapproval changes in accordance with Section 506A. The guidance covers recommended reporting categories for postapproval changes for drugs, other than specified biotechnology and specified synthetic biological products. Recommendations are provided for postapproval changes in (1) components and composition, (2) manufacturing sites, (3) manufacturing process, (4) specifications, (5) package, (6) labeling, (7) miscellaneous changes, and (8) multiple related changes.

Recommendations on reporting categories for changes relating to specified biotechnology and specified synthetic biological products regulated by CDER are found in the guidance for industry entitled *Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products* (July 1997).[3]

This guidance does not provide recommendations on the specific information that should be developed by an applicant to assess the effect of the change on the identity, strength (e.g., assay, content uniformity), quality (e.g., physical, chemical, and biological properties), purity (e.g., impurities and degradation products), or potency (e.g., biological activity, bioavailability, bioequivalence) of a product

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[1] This guidance has been prepared under the direction of the Chemistry, Manufacturing and Controls Coordinating Committee in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance represents the Agency's current thinking on how it will apply the requirements of section 506A of the Act for NDA and ANDA products. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes, regulations, or both.

[2] Pub. L. 105-l 15.

[3] FDA is currently revising the 1997 guidance and intends to issue it in draft for public comment.

as they may relate to the safety or effectiveness of the product. An applicant should consider all relevant CDER guidance documents for recommendations on the information that should be submitted to support a given change.[4]

CDER has published guidances, including the SUPAC (scale-up and postapproval changes) guidances, that provide recommendations on reporting categories. To the extent that the recommendations on ***reporting categories*** in this guidance are found to be inconsistent with guidances published before this guidance was finalized, the recommended reporting categories in such previously published guidances are superseded by this guidance. This guidance does not provide extensive recommendations on reporting categories for components and composition changes (see section V). Therefore, recommended reporting categories for components and composition changes provided in previously published guidances, such as the SUPAC guidances, still apply. Section 506A of the Act provides for two types of changes being effected supplements (see section II) while previously there was only one type. It is important for applicants to use this guidance to determine which type of changes being effected supplement is recommended. CDER intends to update the previously published guidances to make them consistent with this guidance.

If guidance for either recommended filing categories and/or information that should be submitted to support a particular change is not available, the appropriate CDER chemistry or microbiology review staff can be consulted for advice.

II. REPORTING CATEGORIES

Section 506A of the Act provides for four reporting categories that are distinguished in the following paragraphs.

A ***major change*** is a change that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product (506A(c)(2)). A major change requires the submission of a supplement and approval by FDA prior to distribution of the product made using the change (506A(c)(1)). This type of supplement is called, and should be clearly labeled, a ***Prior Approval Supplement.*** An applicant may ask FDA to expedite its review of a prior approval supplement for public health reasons (e.g., drug shortage) or if a delay in making the change described in it would impose an extraordinary hardship on the applicant. This type of supplement is called, and should be clearly labeled, a *Prior Approval Supplement — Expedited Review Requested.'* Requests for expedited review based on extraordinary hardship should

[4] A list of CDER guidances is available on the Internet at http://www.fda.gov/cder/guidance/index.htm.

[5] Internal Agency policies and procedures relating to processing requests for expedited review of supplements to approved ANDAs and NDAs are documented in CDER's Manual of Policies and Procedures (MAPP) at 5240.1 and 5310.3, respectively. MAPPs can be located on the Internet at

be reserved for manufacturing changes made necessary by catastrophic events (e.g., fire) or by events that could not be reasonably foreseen and for which the applicant could not plan.

A ***moderate change*** is a change that has a moderate potential to have an adverse effect on the identity; strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product. There are two types of moderate change. One type of moderate change requires the submission of a supplement to FDA at least 30 days before the distribution of the product made using the change (506A(d)(3)(B)(i)). This type of supplement is called, and should be clearly labeled, a ***Supplement — Changes Being Effected in 30 Days.*** The product made using a moderate change cannot be distributed if FDA informs the applicant within 30 days of receipt of the supplement that a prior approval supplement is required (506A(d)(3)(B)(i)). For each change, the supplement must contain information determined by FDA to be appropriate and must include the information developed by the applicant in assessing the effects of the change (506A(b)). If FDA informs the applicant within 30 days of receipt of the supplement that information is missing, distribution must be delayed until the supplement has been amended with the missing information.

FDA may identify certain moderate changes for which distribution can occur when FDA receives the supplement (506A(d)(3)(B)(ii)). This type of supplement is called, and should be clearly labeled, a ***Supplement — Changes Being Effected.*** If, after review, FDA disapproves a changes being effected in 30 days supplement or changes being effected supplement, FDA may order the manufacturer to cease distribution of the drugs that have been made using the disapproved change (506A(d)(3)(B)(iii)).

A ***minor change*** is a change that has minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product. The applicant must describe minor changes in its next ***Annual Report*** (506A(d)(1)(A) and (d)(2)).

An applicant can submit one or more protocols (i.e., comparability protocols) describing tests, validation studies, and acceptable limits to be achieved to demonstrate the absence of an adverse effect from specified types of changes. A comparability protocol can be used to reduce the reporting category for specified changes. A proposed comparability protocol should be submitted as a prior approval supplement, if not approved as part of the original application. FDA intends to issue separate guidance on comparability protocols.

III. GENERAL REQUIREMENTS

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http://www.fda.gov/cder/mapp.htm.

Other than for editorial changes in previously submitted information (e.g., correction of spelling or typographical errors, reformatting of batch records), an applicant must notify FDA about each change in each condition established in an approved application beyond the variations already provided for in the application (506A(a)).

An applicant making a change to an approved application under section 506A of the Act must also conform to other applicable laws and regulations, including current good manufacturing practice (CGMP) requirements of the Act (21 U.S.C. 351(a)(2)(B)) and applicable regulations in Title *21* of the *Code of Federal Regulations (e.g., 2* 1 CFR parts 2 10, 211, 3 14). For example, manufacturers must comply with relevant CGMP validation and recordkeeping requirements and ensure that relevant records are readily available for examination by authorized FDA personnel during an inspection.

A changes being effected supplement for labeling changes must include 12 copies of the final printed labeling (21 CFR 3 14.50(e)(2)(ii)).

Except for a supplemental application providing for a change in labeling, an applicant should include a statement in a supplemental application or amendment certifying that the required field copy (21 CFR 3 14.50) of the supplement or amendment has been provided.[6]

IV. ASSESSING THE EFFECT OF MANUFACTURING CHANGES

A. Assessment of the Effects of the Change

A drug made with a manufacturing change, whether a major manufacturing change or otherwise, may be distributed only after the holder validates (i.e., assesses) the effects of the change on the identity, strength, quality, purity, and potency of the product as these factors may relate to the safety or effectiveness of the product (506A(b)).[7] For each change, the supplement or annual report must contain information determined by FDA to be appropriate and must include the information developed by the applicant in assessing the effects of the change (506A(b), (c)(l), (d)(2)(A), and (d)(3)(A)). Recommendations on the type of

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[6] Mailing information for field copies is provided in 21 CFR 3 14.440(a)(4). FDA recommends that the *applicant's home FDA district office* referred to in the regulations be the district office where the applicant's headquarters is located.

[7] *Validate the effects of the change* means to assess the effect of a manufacturing change on the identity, strength, quality, purity, or potency of a drug as these factors relate to the safety or effectiveness of the drug. The term *assess* or *assessment,* as used in this guidance, is not the same as CGMP validation. Unless otherwise specified by FDA, CGMP validation (e.g., process, equipment) data need not be filed in the application but should be retained at the facility and be available for review by FDA at the Agency's discretion. For example, in addition to the information assessing the effects of the change specified in 506A(b) of the Act, validation information on sterilization processes should be submitted in an NDA or ANDA.

information that should be included in a supplemental application or annual report is available in guidance documents. If no guidance is available on the type of information that should be submitted to support a change, the applicant is encouraged to contact the appropriate chemistry or microbiology review staff

1. *Conformance to Specifications*

An assessment of the effect of a change on the identity, strength, quality, purity, or potency of the drug product should include a determination that the drug substance intermediates, drug substance, in-process materials, and/or drug product affected by the change conform to the approved specifications.[8] A *specification* is a quality standard (i.e., tests, analytical procedures, and acceptance criteria) provided in an approved application to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents, and other components, including container closure systems and their components and in-process materials. For the purpose of defining specifications, *acceptance criteria* are numerical limits, ranges, or other criteria for the tests described. Conformance to a specification means that the material, when tested according to the analytical procedures listed in the specification, will meet the listed acceptance criteria.

2. *Additional Testing*

In addition to confirmation that the material affected by manufacturing changes continues to meet its specification, the applicant should perform additional testing, when appropriate, to assess whether the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product have been or will be affected. The assessment should include, as appropriate, evaluation of any changes in the chemical, physical, microbiological, biological, bioavailability, and/or stability profiles. This additional assessment could involve testing of the postchange drug product itself or, if appropriate, the component directly affected by the change. The type of additional testing that an applicant should perform would depend on the type of manufacturing change, the type of drug substance and/or drug product, and the effect of the change on the quality of the product. For example:

- Evaluation of changes in the impurity or degradant profile could first involve profiling using appropriate chromatographic techniques and then, depending on the observed changes in the impurity profile, toxicology tests to qualify a new impurity or degradant or to qualify an impurity that is above a previously

[8] If a specification needs to be revised as a result of the change, this would be considered a multiple change (See sections VIII and XII).

qualified level.[9]

- Evaluation of the hardness or friability of a tablet after certain changes.

- Assessment of the effect of a change on bioequivalence when required under 21 CFR part 320 could include, for example, multipoint and/or multimedia dissolution profiling and/or an in vivo bioequivalence study.

- Evaluation of extractables from new packaging components or moisture permeability of a new container closure system.

An applicant should refer to all relevant CDER guidance documents for recommendations on the information that should be submitted to support a given change. If guidance for information that should be submitted to support a particular change is not available, applicants can consult the appropriate CDER chemistry or microbiology review staff for advice.

B. Equivalence

When testing is performed, the applicant should usually assess the extent to which the manufacturing change has affected the identity, strength, quality, purity, or potency of the drug product. Typically this is accomplished by comparing test results from pre- and postchange material and determining if the test results are equivalent. Simply stated: Is the product made after the change equivalent to the product made before the change? An exception to this general approach is that when bioequivalence should be redocumented for certain ANDA postapproval changes, the comparator should be the reference listed drug. Equivalence comparisons frequently require a criterion for comparison with calculation of confidence intervals relative to a predetermined equivalence interval. For this, as well as for other reasons, *equivalent* does not necessarily mean *identical.* Equivalence may also relate to maintenance of a quality characteristic (e.g., stability) rather than a single performance of a test.

C. Adverse Effect

Sometimes manufacturing changes have an adverse effect on the identity, strength, quality, purity, or potency of the. drug product. In many cases, the applicant chooses not to implement these manufacturing changes, but sometimes the applicant wishes to do so. If an assessment concludes that a change has adversely affected the identity, strength, quality, purity, or potency of the drug product, **the change should be filed in a prior approval supplement,**

[9] Recommendations on identifying, qualifying, and reporting impurities can be found in relevant guidances *(e.g.,* ICH Q3B *Impurities in New Drug Products* (November 1996)).

regardless of the recommended reporting category for the change. For example, a type of process change with a recommended filing category of a supplement — changes being effected in 30 days, could cause a new degradant to be formed that requires qualification and/or identification." However, the applicant's degradation qualification procedures may indicate that there are no safety concerns relating to the new degradant. The applicant should submit this change in a prior approval supplement with appropriate information to support the continued safety and effectiveness of the product. During the review of the prior approval supplement, the FDA will assess the impact of any adverse effect on the product as it may relate to the safety or effectiveness of the product.

Applicants are encouraged to consult with the appropriate CDER chemistry or microbiology review staff if there are any questions on whether a change in a characteristic would be viewed by CDER as adversely affecting the identity, strength, quality, purity, or potency of the product.

V. COMPONENTS AND COMPOSITION

Changes in the qualitative or quantitative formulation, including inactive ingredients, as provided in the approved application, are considered major changes and should be filed in a prior approval supplement, unless exempted by regulation or guidance (506A(c)(2)(A)). The deletion or reduction of an ingredient intended to affect only the color of a product may be reported in an annual report. Guidance on changes in components and composition that may be filed in a changes being effected supplement or annual report is not included in this document because of the complexity of these recommendations, but may be covered in one or more guidance documents describing postapproval changes (e.g., SUPAC documents).

VI. MANUFACTURING SITES[11]

A. General Considerations

CDER should be notified about a change to a different manufacturing site used by an applicant to (1) manufacture or process drug products,[12] in-process materials, drug substances, or drug

[10] Recommendations on identifying, qualifying, and reporting impurities can be found in relevant guidances.

[11] See Attachment A for a discussion of the definition of *same manufacturing site* and ***different*** *manufacturing site.*

[12] Manufacturing or processing drug product would also include the preparation (e.g., sterilization, depyrogenation, irradiation, washing) by the applicant or applicant's contractor of container closure systems or packaging components.

substance intermediates, (2) package drug products, (3) label drug products, and (4) test components, drug product containers, closures, packaging materials, in-process materials, or drug products. Sites include those owned by the applicant or contract sites used by an applicant. Testing sites include those performing physical, chemical, biological, and microbiological testing to monitor, accept, or reject materials, as well as those performing stability testing. Sites used to label drug products are considered those that perform labeling of the drug product's primary or secondary packaging components. Sites performing operations that place identifying information on the dosage form itself (e.g., ink imprint on a filled capsule) are considered to be facilities that manufacture or process the drug product. The supplement or annual report should identify whether the proposed manufacturing site is an alternative or replacement to those provided for in the approved application.

A move to a different manufacturing site, when it is a type of site routinely subject to FDA inspection, should be filed as a prior approval supplement if the site does not have a ***satisfactory CGMP inspection***[13] for the ***type of operation***[14] being moved (see sections VI.B. 1 and 2).

For labeling, secondary packaging, and testing site changes, the potential for adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product is considered to be independent of the type of drug product dosage form or specific type of operation being performed. Therefore, the recommended reporting category for any one of these manufacturing site changes will be the same for all types of drug products and operations. For manufacturing sites used to (1) manufacture or process drug products, in-process materials, drug substances, or drug substance intermediates or (2) perform primary packaging operations, the potential for adverse impact and, consequently, the recommended reporting category depends on various factors such as the type of product and operation being performed. For this reason, recommended reporting categories may differ depending on the type of drug product and operations.

Except for those situations described in sections VI.B.4, VI.C.l.b, and VI.D.5, moving production operations between buildings at the same manufacturing site or within a building, or construction activities occurring at a manufacturing site, do not have to be reported to CDER.

A move to a different manufacturing site that involves other changes (e.g., process, equipment) should be evaluated as a multiple related change (see section XII) to determine the appropriate reporting category.

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[13] See Glossary for a definition of *satisfactory CGMP inspection.*

[14] See Attachment B for a discussion of the term *type ofoperation.*

B. Major Changes (Prior Approval Supplement)

The following are examples of changes that are considered to have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

1. A move to a different manufacturing site, except one used to manufacture or process a drug substance intermediate, when the new manufacturing site has never been inspected by FDA for the type of operation that is being moved or the move results in a restart at the new manufacturing site of a type of operation that has been discontinued for more than two years.

2. A move to a different manufacturing site, except those used to manufacture or process a drug substance intermediate, when the new manufacturing site does not have a satisfactory CGMP inspection for the type of operation being moved.

3. A move to a different manufacturing site for (1) the manufacture, processing, or primary packaging of drug products when the primary packaging components control the dose delivered to the patient or the formulation modifies the rate or extent of availability of the drug, or (2) the manufacture or processing of in-process materials with modified-release characteristics. Examples of these types of drug products include modified-release solid oral dosage forms,[15] transdermal systems, liposomal products, depot products, oral and nasal metered-dose inhalers (MDIs), dry powder inhalers (DPIs), and nasal spray pumps.

4. Transfer of manufacturing of an aseptically processed sterile drug substance or aseptically processed sterile drug product to (1) a newly constructed or refurbished aseptic processing facility or area or (2) an existing aseptic processing facility or area that does not manufacture similar (including container types and sizes) approved products. For example, transferring the manufacture of a lyophilized product to an existing aseptic process area where no approved lyophilized products are manufactured or the approved lyophilized products being manufactured have dissimilar container types and/or sizes to the product being transferred. See section VI.C.1.b for recommendations for other manufacturing site changes relating to aseptically processed sterile drug substance or aseptically processed sterile drug product.

[15] Certain operations relating to the manufacture, processing, or primary packaging of modified-release solid oral dosage form products need not be reported in a prior approval supplement (see sections VI.C.1.c and VI.D.6).

5. Transfer of the manufacture of a finished product sterilized by terminal processes to a newly constructed facility at a different manufacturing site. Once this change has been approved, subsequent site changes to the facility for similar product types and processes may be filed as a supplement — changes being effected in 30 days (see section VI.C. 1 .a).

C. Moderate Changes (Supplement — Changes Being Effected)

The following are examples of changes that are considered to have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

The following manufacturing site changes (excluding changes relating to drug substance intermediate manufacturing sites) should be filed in a prior approval supplement if the new site does not have a satisfactory CGMP inspection for the type of operation being moved (see sections VI.B. 1 and 2).

1. *Supplement — Changes Being Effected in 30 Days*

   a. A move to a different manufacturing site for the manufacture or processing of any drug product, in-process material, or drug substance that is not otherwise provided for in this guidance.

   b. For aseptically processed sterile drug substance or aseptically processed sterile drug product, a move to an aseptic processing facility or area at the same or different manufacturing site, except as provided for in section VI.B.4.

   c. A move to a different manufacturing site for the primary packaging of (1) any drug product that is not otherwise listed as a major change and (2) modified-release solid oral dosage form products.

   d. A move to a different manufacturing site for testing if (1) the test procedures approved in the application or procedures that have been implemented via an annual report are used, (2) all postapproval commitments made by the applicant relating to the test procedures have been fulfilled (e.g., providing methods validation samples), and (3) the new testing facility has the capability to perform the intended testing.

2. *Supplement — Changes Being Effected*

a. A move to a different manufacturing site for the manufacture or processing of the final intermediate.

D. Minor Changes (Annual Report)

The following are examples of changes that are considered to have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

The following manufacturing site changes (excluding changes relating to drug substance intermediate manufacturing sites) should be filed in a prior approval supplement if the new site does not have a satisfactory CGMP inspection for the type of operation being moved (see sections VI.B. 1 and 2).

1. A move to a different manufacturing site for secondary packaging.

2. A move to a different manufacturing site for labeling.

3. A move to a different manufacturing site for the manufacture or processing of drug substance intermediates, other than the final intermediate.

4. A change in the contract sterilization site for packaging components when the process is not materially different from that provided for in the approved application and the facility has a satisfactory CGMP inspection for the type of operation being performed.

5. A transfer of the manufacture of a finished product sterilized by terminal processes to a newly constructed building or existing building at the same manufacturing site.

6. A move to a different manufacturing site for the ink imprinting of solid oral dosage form products.

VII. MANUFACTURING PROCESS

A. General Considerations

The potential for adverse effects on the identity, strength, quality, purity, or potency of a drug product as they may relate to the safety or effectiveness of the product depends on the type of manufacturing process and the changes being instituted for the drug substance or drug product.

In some cases there may be a substantial potential for adverse effect, regardless of direct testing of the drug substance or drug product for conformance with the approved specification. When there is a substantial potential for adverse effects, a change should be filed in a prior approval supplement.

B. Major Changes (Prior Approval Supplement)

The following are examples of changes that are considered to have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

1. Changes that may affect the controlled (or modified) release, metering or other characteristics (e.g., particle size) of the dose delivered to the patient, including the addition or deletion of a code imprint by embossing, debossing, or engraving on a modified-release solid oral dosage form.

2. Changes that may affect product sterility assurance including, where appropriate, process changes for sterile drug substances and sterile packaging components. These include:

   - Changes in the sterilization method (e.g., gas, dry heat, irradiation). These include changes from sterile filtered or aseptic processing to terminal sterilization, or vice versa.
   - Addition, deletion, or substitution of sterilization steps or procedures for handling sterile materials in an aseptic processing operation.
   - Replacing sterilizers that operate by one set of principles with sterilizers that operate by another principle (e.g., substituting a gravity displacement steam process with a process using superheated water spray).
   - Addition to an aseptic processing line of new equipment made of different materials (e.g., stainless steel versus glass, changes between plastics) that will come in contact with sterilized bulk solution or sterile drug components, or deletion of equipment from an aseptic processing line.
   - Replacing a Class 100 aseptic fill area with a barrier system or isolator for aseptic filling. Once this change has been approved, subsequent process changes for similar product types in the same barrier system or isolator may be filed as a Supplement — changes being effected in 30 days.
   - Replacement or addition of lyophilization equipment of a different size that uses different operating parameters or lengthens the overall process

time.

- Changes from bioburden-based terminal sterilization to the use of an overkill process, and vice versa.
- Changes to aseptic processing methods, including scale, that extend the total processing, including bulk storage time, by more than 50 percent beyond the validated limits in the approved application.
- Changes in sterilizer load configurations that are outside the range of previously validated loads.
- Changes in materials or pore size rating of filters used in aseptic processing.

3. The following changes for a natural product?

- Changes in the virus or adventitious agent removal or inactivation methods. This is applicable to any material where such procedures are necessary, including drug substance, drug product, reagents, and excipients.
- For drug substance and drug product, changes in the source material (e.g., microorganism, plant) or cell line.
- For drug substance and drug product, establishment of a new master cell bank or seed.

4. Any fundamental change in the manufacturing process or technology from that currently used by the applicant. For example:

a. Drug product

- Dry to wet granulation or vice versa.
- Change from one type of drying process to another (e.g., oven tray, fluid bed, microwave).

b. Drug substance

- Filtration to centrifugation or vice versa.
- Change in the route of synthesis of a drug substance.

5 . The following changes for drug substance

[16] For the purposes of this guidance, *naturalproduct* refers to materials (e.g., drug substance, excipients) that are derived from plants, animals, or microorganisms. The specific recommendations for natural products are not applicable to inorganic compounds (e.g., salts, minerals).

- Any process change made after the final intermediate processing step in drug substance manufacture.
- Changes in the synthesis or manufacture of the drug substance that may affect its impurity profile and/or the physical, chemical, or biological properties.

6. Addition of an ink code imprint or change to or in the ink used for an existing imprint code for a solid oral dosage form drug product when the ink as changed is not currently used on ***CDER-approvedproducts."***

7. Establishing a new procedure for reprocessing a batch of drug substance or drug product that fails to meet the approved specification.

C. Moderate Changes (Supplement — Changes Being Effected)

The following are examples of changes that are considered to have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

1. Supplement — Changes Being Effected in 30 Days

a. For drug products, any change in the process, process parameters and/or equipment, except as otherwise provided for in this guidance.

b. For drug substances, any change in process and/or process parameters, except as otherwise provided for in this guidance.

c. For natural protein drug substances and drug products:

- Any change in the process, process parameters, and/or equipment, except as otherwise provided for in this guidance.
- An increase or decrease in production scale during finishing steps that involves new or different equipment.
- Replacement of equipment with that of similar, but not identical, design and operating principle that does not affect the process methodology or process operating parameters.

d. For sterile products, drug substances, and components, as appropriate:

[17] See Attachment C for a discussion of *CDER-approved.*

- Changes in dry heat depyrogenation processes'for glass container systems for products that are produced by terminal sterilization processes or aseptic processing.
- Changes to filtration parameters for aseptic processing (including flow rate, pressure, time, or volume, but not filter materials or pore size rating) that require additional validation studies for the new parameters.

a Filtration process changes that provide for a change from single to dual product sterilizing filters in series, or for repeated filtration of a bulk.

- Changes from one qualified sterilization chamber to another for in-process or terminal sterilization that results in changes to validated operating parameters (time, temperature, F,, and others).
- Changes in scale of manufacturing for terminally sterilized products that increase the bulk solution storage time by more than 50 percent beyond the validated limits in the approved application when bioburden limits are unchanged.

e. For drug substances, redefinition of an intermediate, excluding the final intermediate, as a starting material.

2. Supplement — Changes Being Effected

a. A change in methods or controls that provides increased assurance that the drug substance or drug product will have the characteristics of identity, strength, purity, or potency that it purports or is represented to possess.

b. For sterile drug products, elimination of in-process filtration performed as part of the manufacture of a terminally sterilized product.

D. Minor Changes (Annual Report)

The following are examples of changes that are considered to have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

1. For drug products and protein drug substances, changes to equipment of the same design and operating principle and/or changes in scale, except as otherwise provided for in this guidance (e.g., section VII.C. 1 .c).

2. A minor change in an existing code imprint for a dosage form. For example, changing from a numeric to alphanumeric code.

3. Addition of an ink code imprint or a change in the ink used in an existing code imprint for a solid oral dosage form drug product when the ink is currently used on CDER-approved products.

4. Addition or deletion of a code imprint by embossing, debossing, or engraving on a solid dosage form drug product other than a modified- release dosage form.

5. A change in the order of addition of ingredients for solution dosage forms or solutions used in unit operations (e.g., granulation solutions).

6. Changes in scale of manufacturing for terminally sterilized products that increase the bulk solution storage time by no more than 50 percent beyond the validated limits in the approved application when bioburden limits are unchanged.

VIII. SPECIFICATIONS

A. General Considerations

All changes in specifications from those in the approved application must be submitted in a prior approval supplement unless otherwise exempted by regulation or guidance (506A(c)(2)(A)). *Specifications* (i.e., tests, analytical procedures, and acceptance criteria) are the quality standards provided in an approved application to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents, and other components, including container and closure systems and in-process materials. For the purpose of defining specifications, *acceptance criteria* are numerical limits, ranges, or other criteria for the tests described. An example of a test, analytical procedure, and acceptance criteria is: assay, a specific fully described high pressure liquid chromatography (HPLC) procedure, and 98.0-102.0 percent. The recommendations in this section. also apply to specifications associated with sterility assurance that are included in NDA and ANDA submissions.[18]

A *regulatory* analytical procedure is the analytical procedure used to evaluate a defined characteristic of the drug substance or drug product. The analytical procedures in the U.S.

[18] See FDA guidance for industry on the *Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products* (November 1994).

Pharmacopeia/National Formulary (USP/NF) are those legally recognized under section 50 1 (b) of the Act as the regulatory analytical procedures for compendia1 items.

The applicant may include in its application *alternative* analytical procedures to the approved regulatory procedure for testing the drug substance and drug product. However, for purposes of determining compliance with the Act, the regulatory analytical procedure is used.

In sections B-D below, the use of the term *analytical procedure* without a qualifier such as *regulatory* or *alternative* refers to analytical procedures used to test materials other than the drug substance or drug product.

B. Major Changes (Prior Approval Supplement)

The following are examples of changes in specifications that are considered to have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

1. Relaxing an acceptance criterion, except as otherwise provided for in this guidance (e.g., section VIII.C. 1 .b).

2. Deleting any part of a specification, except as otherwise provided for in this guidance (e.g., section VIII.D.2).

3. Establishing a new regulatory analytical procedure.

4. A change in a regulatory analytical procedure that does not provide the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the regulatory analytical procedure described in the approved application.

5. A change in an analytical procedure used for testing components, packaging components, the final intermediate, in-process materials after the final intermediate, or starting materials introduced after the final intermediate that does not provide the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application, except as otherwise noted. For example, a change from an HPLC procedure that distinguishes impurities to (1) one that does not, (2) another type of analytical procedure (e.g., titrimetric) that does not, or (3) one that distinguishes impurities but the limit of detection and/or limit of quantitation is higher.

6. Relating to testing of raw materials for viruses or adventitious agents:[19] (1) relaxing an acceptance criteria, (2) deleting a test, or (3) a change in the analytical procedure that does not provide the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application.

C. Moderate Changes (Supplement — Changes Being Effected)

The following are examples of changes in specifications that are considered to have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

1. Supplement — Changes Being Effected in 30 Days

a. Any change in a regulatory analytical procedure other than editorial or those identified as major changes.

b. Relaxing an acceptance criterion or deleting a test for raw materials used in drug substance manufacturing, in-process materials prior to the final intermediate, starting materials introduced prior to the final drug substance intermediate, or drug substance intermediates (excluding final intermediate), except as provided for in section VIII.B.6.

c. A change in an analytical procedure used for testing raw materials used in drug substance manufacturing, in-process materials prior to the intermediate, starting materials introduced prior to the final drug substance intermediate, or drug substance intermediates (excluding final intermediate) that does not provide the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application, except as provided for in section VIII.B.6.

d. Relaxing an in-process acceptance criterion associated with microbiological monitoring of the production environment, materials, and components that are included in NDA and ANDA submissions. For example, increasing the microbiological alert or action limits for critical processing environments in an aseptic fill facility or increasing the acceptance limit for bioburden in bulk solution intended for filtration and

[19] In this context, testing for adventitious agents is not considered to include tests that are found in an official compendium (e.g., USP <61>).

aseptic filling.

2. *Supplement — Changes Being Effected*

a. An addition to a specification that provides increased assurance that the drug substance or drug product will have the characteristics of identity, strength, purity, or potency that it purports or is represented to possess. For example, adding a new test and associated analytical procedure and acceptance criterion.

b. A change in an analytical procedure used for testing components, packaging components, the final intermediate, in-process materials after the final intermediate, or starting materials introduced after the final intermediate that provides the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application.

D. Minor Changes (Annual Report)

The following are examples of changes in specifications that are considered to have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

1. Any change in a specification made to comply with an official compendium.

2. For drug substance and drug product, the addition, deletion or revision of an alternative analytical procedure that provides the same or greater level of assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application.

3. Tightening of acceptance criteria.

4. A change in an analytical procedure used for testing raw materials used in drug substance synthesis, starting materials introduced prior to the final drug substance intermediate, in-process materials prior to the final intermediate, or drug substance intermediates (excluding final intermediate) that provides the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application.

IX. PACKAGE

A. General Considerations

The potential for adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product when making a change to or in the container closure system is generally dependent on the route of administration of the drug product, performance of the container closure system, and the likelihood of interaction between the packaging component and the dosage form. In some cases there may be a substantial potential for adverse effect, regardless of direct product testing for conformance with the approved specification.

A change to or in a packaging component will often result in a new or revised specification for the packaging component. This situation does not have to be considered a multiple related change. Only the reporting category for the packaging change needs to be considered.

B. Major Changes (Prior Approval Supplement)

The following are examples of changes that are considered to have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

1. For liquid (e.g., solution, suspension, elixir) and semisolid (e.g., creams, ointments) dosage forms, a change to or in polymeric materials (e.g., plastic, rubber) of primary packaging components, when the composition of the component as changed has never been used in a CDER-approved product of the same dosage form and same route of administration. For example, a polymeric material that has been used in a CDER-approved topical ointment would not be considered CDER-approved for use with an ophthalmic ointment.

2. For liquid (e.g., solution, suspension, elixir) and semisolid (e.g., creams, ointments) dosage forms in permeable or semipermeable container closure systems, a change to an ink and/or adhesive used on the permeable or semipermeable packaging component to one that has never been used in a CDER-approved product of the same dosage form, same route of administration, ***and*** same type of permeable or semipermeable packaging component (e.g., low density polyethylene, polyvinyl chloride).

3. A change in the primary packaging components for any product when the primary packaging components control the dose delivered to the patient (e.g., the valve or actuator of a metered-dose inhaler).

4. For sterile products, any other change that may affect product sterility assurance such as:[20]

- A change from a glass ampule to a glass vial with an elastomeric closure.
- A change to a flexible container system (bag) from another container system.
- A change to a prefilled syringe dosage form from another container system.
- A change from a single unit dose container to a multiple dose container system.
- Changes that add or delete silicone treatments to container closure systems (such as elastomeric closures or syringe barrels).
- Changes in the size and/or shape of a container for a sterile drug product.

5. Deletion of a secondary packaging component intended to provide additional protection to the drug product (e.g., carton to protect from light, over-wrap to limit transmission of moisture or gases).

6. A change to a new container closure system if the new container closure system does not provide the same or better protective properties than the approved container closure system.

C. Moderate Changes (Supplement — Changes Being Effected)

The following are examples of changes that are considered to have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

1. *Supplement — Changes Being Effected in 30 Days*

a. A change to or in a container closure system, except as otherwise provided for in this guidance.

b. Changes in the size or shape of a container for a sterile drug substance.

[20] Some of these identified changes, depending on the circumstances, may have to be filed as new NDAs or ANDAs instead of as supplements. Applicants can consult the appropriate CDER chemistry division/office if there are questions.

2. *Supplement — Changes Being Effected*

a. A change in the size and/or shape of a container for a nonsterile drug product, except for solid dosage forms (see section IX.D.2 regarding solid dosage forms).

b. A change in or addition or deletion of a desiccant.

D. Minor Changes (Annual Report)

The following are examples of changes that are considered to have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

1. A change in the container closure system for a nonsterile drug product, based on a showing of equivalency to the approved system under a protocol approved in the application or published in an official compendium.

2. A change in the size and/or shape of a container containing the same number of dose units, for a nonsterile solid dosage form.

3. The following changes in the container closure system of solid oral dosage form products as long as the new package provides the same or better protective properties (e.g., light, moisture) and any new primary packaging component materials have been used in and been in contact with CDER-approved solid oral dosage form products:[21]

- Adding or changing a child-resistant closure, changing from a metal to plastic screw cap, or changing from a plastic to metal screw cap.
- Changing from one plastic container to another of the same type of plastic (e.g., high density polyethylene (HDPE) container to another HDPE container).
- Changes in packaging materials used to control odor (e.g., charcoal packets).
- Changes in bottle filler (e.g., change in weight of cotton or amount used) without changes in the type of filler (e.g., cotton to rayon).

[21] For sections IX.D.3 to 6, changes in the container closure system that result in product contact with a component material that has never been used in any CDER-approved product of the same type should be filed as a supplement — changes being effected in 30 days (IX.C.1) or prior approval supplement (IX.B.1).

- Increasing the wall thickness of the container.
- A change in or addition of a cap liner.
- A change in or addition of a seal (e.g., heat induction seal).
- A change in an antioxidant, colorant, stabilizer, or mold releasing agent for production of the container and/or closure to one that is used at similar levels in the packaging of CDER-approved solid oral dosage form products.
- A change to a new container closure system when the container closure system is already approved in the NDA or ANDA for other strengths of the product.

4. The following changes in the container closure system of nonsterile liquid products, as long as the new package provides the same or better protective properties and any new primary packaging component materials have been used in and been in contact with CDER-approved liquid products with the same route of administration (i.e., the material in contact with a liquid topical should already have been used with other CDER-approved liquid topical products):

   - Adding or changing a child-resistant closure, changing from a metal to plastic screw cap, or changing from a plastic to metal screw cap.
   - Increasing the wall thickness of the container.
   - A change in or addition of a cap liner.
   - A change in or addition of a seal (e.g., heat induction seal).

5. A change in the container closure system of unit dose packaging (e.g., blister packs) for nonsterile solid dosage form products, as long as the new package provides the same or better protective properties and any new primary packaging component materials have been used in and been in contact with CDER-approved products of the same type (e.g., solid oral dosage form, rectal suppository).

6. The following changes in the container closure system of nonsterile semisolid products, as long as the new package provides the same or better protective properties and any new primary packaging component materials have been used in and been in contact with CDER-approved semisolid products:

   - Changes in the closure or cap.
   - Increasing the wall thickness of the container.
   - A change in or addition of a cap liner.
   - A change in or addition of a seal.

- A change in the crimp sealant.

7. A change in the flip seal cap color, as long as the cap color is consistent with any established color coding system for that class of drug products.

X. LABELING

A. General Considerations

A drug product labeling change includes changes in the package insert, package labeling, or container label. An applicant should promptly revise all promotional labeling and drug advertising to make it consistent with any labeling change implemented in accordance with the regulations. All labeling changes for ANDA products must be consistent with section 505(j) of the Act.

B. Major Changes (Prior Approval Supplement)

Any proposed change in the labeling, except those that are designated as moderate or minor changes by regulation or guidance, should be submitted as a prior approval supplement. The following list contains some examples of changes that are currently considered by CDER to fall into this reporting category.

1. Changes based on postmarketing study results, including, but not limited to, labeling changes associated with new indications and usage.

2. Change in, or addition of, pharmacoeconomic claims based on clinical studies.

3. Changes to the clinical pharmacology or the clinical study section reflecting new or modified data.

4. Changes based on data from preclinical studies.

5. Revision (expansion or contraction) of population based on data.

6. Claims of superiority to another product.

7. Change in the labeled storage conditions, unless exempted by regulation or guidance.

C. Moderate Changes (Supplement — Changes Being Effected)

A changes being effected supplement should be submitted for any labeling change that (1) adds or strengthens a contraindication, warning, precaution, or adverse reaction, (2) adds or strengthens a statement about drug abuse, dependence, psychological effect, or overdosage, (3) adds or strengthens an instruction about dosage and administration that is intended to increase the safe use of the product, (4) deletes false, 'misleading, or unsupported indications for use or claims for effectiveness, or (5) is specifically requested by FDA. The submission should include 12 copies of final printed labeling. The following list includes some examples of changes that are currently considered by CDER to fall into this reporting category.

1. Addition of an adverse event due to information reported to the applicant or Agency.

2. Addition of a precaution arising out of a postmarketing study.

3. Clarification of the administration statement to ensure proper administration of the product.

4. Labeling changes, normally classified as major changes, that FDA specifically requests be implemented using a changes being effected supplement.

D. Minor Changes (Annual Report)

Labeling with editorial or similar minor changes or with a change in the information concerning the description of the drug product or information about how the drug is supplied that does not involve a change in the dosage strength or dosage form should be described in an annual report. The following list includes some examples that are currently considered by CDER to fall into this reporting category.

1. Changes in the layout of the package or container label that are consistent with FDA regulations (e.g., 21 CFR part 201), without a change in the content of the labeling.

2. Editorial changes, such as adding a distributor's name.

3. Foreign language versions of the labeling, if no change is made to the content of the approved labeling and a certified translation is included.

4. Labeling changes made to comply with an official compendium.

XI. MISCELLANEOUS CHANGES

A. Major Changes (Prior Approval Supplement)

The following are examples of changes that are considered to have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

1. Changes requiring completion of studies in accordance with 2 1 CFR part 320 to demonstrate equivalence of the drug to the drug as manufactured without the change or to a reference listed drug (506A(c)(2)(B)).

2. Addition of a stability protocol or comparability protocol.

3. Changes to an approved stability protocol or comparability protocol unless otherwise provided for in this guidance (e.g., VIII.C, VIII.D, XI.C.2).

4. An extension of an expiration dating period based on (1) data obtained under a new or revised stability testing protocol that has not been approved in the application or (2) full shelf life data on pilot scale batches using an approved protocol.

B. Moderate Changes (Supplement — Changes Being Effected)

The following are examples of changes that are considered to have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

I. *Supplement — Changes Being Effected in 30 Days*

a. Reduction of an expiration dating period to provide increased assurance of the identity, strength, quality, purity, or potency of the drug product. Extension of an expiration date that has previously been reduced under this provision should be filed in a supplement — changes being effected in 30 days even if it is based on data obtained under a protocol approved in the application.

2. *Supplement — Changes Being Effected*

No changes have been identified.

C. Minor Changes (Annual Report)

The following are examples of changes that are considered to have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

1. An extension of an expiration dating period based on full shelf life data on full production batches obtained under a protocol approved in the application.

2. Addition of time points to the stability protocol or deletion of time points beyond the approved expiration dating period.

3. A change from previously approved stability storage conditions to storage conditions recommended in International Conference on Harmonisation (ICH) guidances.

4. Non-USP reference standards:

   - Replacement of an in-house reference standard or reference panel (or panel member) according to procedures in an approved application.
   - Tightening of acceptance criteria for existing reference standards to provide greater assurance of product purity and potency.

XII. MULTIPLE RELATED CHANGES

Multiple related changes involve various combinations of individual changes. For example, a site change may also involve equipment and manufacturing process changes or a components and composition change may necessitate a change in a specification. For multiple related changes where the recommended reporting categories for the individual changes differ, CDER recommends that the filing be in accordance with the most restrictive of those recommended for the individual changes. When the multiple related changes all have the same recommended reporting category, CDER recommends that the filing be in accordance with the reporting category for the individual changes.

ATTACHMENT A
MANUFACTURING SITES

All owners or operators of all drug establishments (not exempt by regulation) that engage in the manufacture, preparation, propagation, compounding, or processing of a drug or drugs are required to register with the FDA (2 1 CFR 207.20). *An establishment* means a place of business under one management at one general physical location (21 CFR 207.3(a)(7)). A *generalphysical location* is reasonably construed to include separate buildings within the same city *if* the activities in them are closely related to the same business enterprise, under the supervision of the same local management, and all inspected at the same time (ORA Field Management Directive No. 132).

For the purposes of determining the reporting category for moves between buildings, the terms *different manufacturing site* and *same manufacturing site* mean:

Domestic Establishments

Same manufacturing site:

- The new and old building are included under the same drug establishment registration number[22]

  and

- The same FDA district office is responsible for inspecting the operations in both the new and old building.

Different manufacturing site:

- The new and old building have different drug establishment registration numbers

  or

- Different FDA district offices are responsible for inspecting operations in the new and old building.

For domestic establishments, the terms *same* and *different manufacturing site* supersede the terms *contiguous campus, same campus,* and *different campus* as used in the SUPAC guidances.

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[22] The registration number is the number assigned to the establishment by the district (ORA Field Management Directive No. 92). Currently, the registration number is the seven digit central file number (CFN).

Foreign Establishments

Foreign establishments are not currently required to register with the FDA. On May 14, 1999 FDA published a proposed rule to require registration of foreign establishments (64 FR 26330). Until the time registration of foreign establishments is required, same and different manufacturing sites mean:

Same manufacturing site:

- A contiguous or unbroken site or a set of buildings in adjacent city blocks.

Different manufacturing site:

- New and old building not on a contiguous site or not in adjacent city blocks.

ATTACHMENT B
TYPE OF OPERATION AND CGMP INSPECTIONS

Section VI states that a change to a different manufacturing site should be filed in a prior approval supplement when (1) the new manufacturing site has never been inspected by FDA for the type of operation being moved, (2) the move results in a restart at the new manufacturing site of a type of operation that has been discontinued for more than two years, or (3) the new manufacturing site does not have a satisfactory current good manufacturing practice (CGMP) inspection for the type of operation being moved.

A *profile class system* is used by FDA to assist in (1) managing the CGMP inspection process, (2) evaluating the findings and the compliance follow-up needed, and (3) communicating the results of inspections. A profile class can relate to the manufacture of a particular dosage form (e.g., large volume parenterals, oral liquids), type of drug substance (e.g., sterile bulk by chemical synthesis), or specific function performed at a site (e.g., control testing laboratory). There are profile class codes for major categories of drug substance processes, dosage forms, and manufacturing functions (see table below). However, the system is not comprehensive for all operations performed in the pharmaceutical industry (see not elsewhere classified (NEC) profile class code).

The term *type of operation* refers to the specialized or even unique conditions and practices which are employed to manufacture a class or category of drug substance or drug product or to perform a limited segment of the manufacturing process. These conditions and practices exist and are performed within the framework of CGMPs, along with general conditions and practices that contribute to the manufacture of all products at a given manufacturing site. Both the general and the specific conditions and practices are inspected to evaluate the CGMP acceptability of a manufacturing site. A wide variety of classes or categories of drug substances and products may be produced at a manufacturing site or the manufacturing site may only produce a single class of drug substance and/or drug product or perform a limited segment of a manufacturing process. Each type of operation is represented by a ***profile class code.***

Generally, a satisfactory CGMP rating for a profile class code is used to communicate a satisfactory CGMP clearance for all of the products and for all of the operations included within the category that code represents. Thus the profile class code for a particular dosage form or type of drug substance is used to communicate the CGMP status for all aspects of manufacturing, processing, packing, or holding that are performed at the specific manufacturing site relating to that particular dosage form or type of drug substance, including packaging and labeling operations, testing, and quality control. The profile class code for a particular dosage form or type of drug substance is also used to communicate the CGMP status for manufacturing sites that produce &process material (e.g., controlled-release beads), package drug products, or label drug products, even if these are stand-alone (e.g., contractor) operations.

A few profile class codes that describe certain types of operations (see items in boldface in table) are provided to report the CGMP status for contractor firms whose only function in the manufacturing process is to perform this operation. If one of these operations (e.g., steam sterilization process) is performed at the manufacturing site involved in producing the drug product/drug substance, the CGMP status for that operation is reported-as part of the profile class code for the particular dosage form or type of drug substance. For example, a manufacturing site producing a terminally sterilized small volume parenteral product would be reported with the profile class code for the dosage form (SVT), not by the profile code for the sterilization process (SSP).

Certain inspections may be required by program priorities even if a profile class code indicates an acceptable CGMP status. The current profile codes/classes for human drugs are:

ADM	Aerosol dispensed medication	NEC	Not elsewhere classified (when using this class, specific products are noted)
CBI	Biotechnology crude drug	OIN	Ointment, nonsterile (includes cream, jelly, paste)
CEX	Plant/animal extraction crude drug	POW	Powders (includes oral and topical)
CFS	Sterile bulk by fermentation crude drug	RAD	Radiopharmaceutical
CFN	Nonsterile bulk by fermentation crude drug	**RSP**	**Radiation sterilization process**
CHG	Capsule, prompt release	SNI	Sterile noninjectable
CRU	Crude bulk drugs-nonsynthesized	SOP	Soap
CSG	Capsules, soft gelatin	**SSP**	**Steam sterilization process**
CSN	Nonsterile bulk by chemical synthesis	SUP	Suppositories
CSP	**Chemical sterilization process**	**SVL**	Small volume parenterals (lyophilized)
c s s	Sterile bulk by chemical synthesis	s v s	Sterile-filled small volume parenterals
CTL	**Control testing laboratories**	SVT	Terminally sterilized small volume parenteral
CTR	Capsules, modified-release	TCM	Tablets, prompt-release
GAS	Medical gas (includes liquid oxygen and other)	TCT	Tablets, delayed-release
GSP	**Gas sterilization process**	TDP	Transdermal patches
HSP	**Dry heat sterilization process**	**TSP**	**Fractional (tyndallization) sterilization process**
LIQ	Liquid (includes solutions, suspension, elixirs, and tinctures)	TTR	Tablets, extended-release
LVP	Large volume parenterals	**WSP**	**Water sterilization process**

CGMP inspectional status, based on the profile class, is available through FDA's Freedom of Information (FOI) Office. (See Glossary under Satisfactory Current Good Manufacturing Practice (CGMP) Inspection for more information regarding FOI requests.)

Examples of postapproval manufacturing site changes and filing consequences:

- An applicant wants to move the manufacture of an immediate-release tablet (TCM) to a different manufacturing site that currently manufactures, and has satisfactory CGMP status for, capsules (CHG) and powders for oral solution (POW). This manufacturing site change should be tiled in a prior approval supplement because the new manufacturing site doesn't have a satisfactory CGMP inspection for immediate-release tablets.

- An applicant wants to contract out their packaging operations for immediate-release tablets (TCM) and capsules (CHG), and modified-release capsules (CTR). The potential contract packager has a satisfactory CGMP status for immediate-release and modified-release capsules but has never packaged immediate-release tablets. The packaging site change for the immediate-release tablet products should be filed in a prior approval supplement. The packaging site change for the capsule products should be filed as recommended in section VI of this guidance for packaging sites with a satisfactory CGMP inspection.

- An applicant wishes to consolidate their product testing to a single analytical laboratory at a manufacturing site. This manufacturing site produces various solid oral dosage form products, has an operational analytical laboratory currently at the site, and satisfactory CGMP inspections for the manufacturing occurring at the facility. Some of the products that will be tested at the analytical laboratory when the consolidation occurs are not solid oral dosage form products. Unlike most other production operations, testing laboratories (and other operations in boldface in the table) are not inspected on a dosage form/type of drug substance specific basis. The satisfactory CGMP inspection of the analytical laboratory, which was performed as part of the CGMP inspection for manufacture of the solid oral dosage form products, is considered to apply to all dosage forms, including those not actually produced at the site.

ATTACHMENT C
CDER-APPROVED

In several places throughout the guidance, different reporting categories are proposed for changes to or the addition of certain components based on whether the component/material has been used in and has been in contact with CDER-approved products. Different reporting categories are recommended once CDER has reviewed certain components/materials in association with a product approval because similar subsequent changes then have a reduced potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product. For example, certain changes in the container closure systems of solid oral dosage form products may be included in the annual report, as long as the new package provides the same or better protective properties and any new primary packaging component materials have been used in and been in contact with CDER-approved solid oral dosage form products (see section IX.D.3). If the primary packaging component material has not been used in or has not been in contact with CDER-approved solid oral dosage form products, then submission of the change in an annual report is not recommended.

CDER-approved products are considered those subject to an approved NDA or ANDA. Some information on which components/materials are used in CDER-approved products is available from the Agency (e.g., FDA, CDER, *Inactive Ingredient Guide,* 1996, Division of Drug Information Resources). When information is not available, an applicant should use reliable sources of information to determine that the component or material has been used in and has been in contact with a CDER-approved product of the same dosage form and route of administration, as appropriate. The applicant should identify in the supplement or annual report the basis for the conclusion that the component or material is used in a CDER-approved product.

If an applicant cannot confirm that a component or material has been used in and has been in contact with a CDER-approved product of the same dosage form and route of administration, the applicant has the option of filing the change for a single NDA or ANDA using the higher recommended reporting category and, after approval, filing similar subsequent changes for other NDAs and ANDAs using the lower recommended reporting category.

GLOSSARY

Acceptance Criteria: Numerical limits, ranges, or other criteria for the tests described.

Active Ingredient/Drug Substance: Any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of a disease, or to affect the structure or any function of the human body, but does not include intermediates used in the synthesis of such ingredient. The term includes those components that may undergo chemical change in the manufacture of the drug product and are present in the drug product in a modified form intended to furnish the specified activity or effect (21 CFR 210.3(b)(7) and 314.3).

Container Closure System: The sum of packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection to the drug product.

Component: Any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product (21 CFR 210.3(b)(3)).

Drug Product: A finished dosage form, for example, tablet, capsule, or solution, that contains an active ingredient, generally, but not necessarily, in association with inactive ingredients (2 1 CFR 210,3(b)(4)).

Final Intermediate: The last compound synthesized before the reaction that produces the drug substance. The final step forming the drug substance must involve covalent bond formation or breakage; ionic bond formation (i.e., making the salt of a compound) does not qualify. Consequently, when the drug substance is a salt, the precursors to the organic acid or base, rather than the acid or base itself, should be considered the final intermediate.

Inactive Ingredients: Any intended component of the drug product other than an active ingredient.

In-process Material: Any material fabricated, compounded, blended, or derived by chemical reaction that is produced for, and used in, the preparation of the drug product (21 CFR 210.3(b)(9)). For drug substance, in-process materials are considered those materials that are undergoing change (e.g., molecular, physical).

Intermediate: A material produced during steps of the synthesis of a drug substance that must undergo further molecular change before it becomes a drug substance.

Package: The container closure system and labeling, associated components (e.g., dosing cups, droppers, spoons), and external packaging (e.g., cartons, shrink wrap).

Packaging Component: Any single part of a container closure system.

Primary Packaging Component: A packaging component that is or may be in direct contact with the dosage form.

Reference Listed Drug: The listed drug identified by FDA as the drug product on which an applicant relies in seeking approval of its abbreviated application (21 CFR 3 14.3).

Satisfactory Current Good Manufacturing Practice (CGMP) Inspection: A satisfactory CGMP inspection is an FDA inspection during which (1) no objectionable conditions or practices were found during (No Action Indicated (NAI)) or (2) objectionable conditions were found, but, corrective action is left to the firm to take voluntarily and the objectionable conditions will not be the subject of further administrative or regulatory actions (Voluntary Action Indicated (VAI)).

Information about the CGMP status of a firm may be obtained by requesting a copy of the Quality Assurance Profile (QAP) from the FDA's Freedom of Information (FOI) Office. The QAP reports information on the CGMP compliance status of firms that manufacture, package, assemble, repack, relabel, or test human drugs, devices, biologics, and veterinary drugs. All FOI requests must be in writing and should follow the instructions found in the reference entitled *A Handbookfor Requesting Information and Records from FDA*. An electronic version of this reference is available on the Internet at http://www.fda.gov/opacom/backgrounders/foiahand.html.

Secondary Packaging Component: A packaging component that is not and will not be in direct contact with the dosage form.

Specifications: The quality standards (i.e., tests, analytical procedures, and acceptance criteria) provided in an approved application to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents, and other components including container closure systems, and in-process materials.

Validate the Effects of the Change: To assess the effect of a manufacturing change on the identity, strength, quality, purity, or potency of a drug as these factors relate to the safety or effectiveness of the drug.

Attachment 3

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

November 1, 1999

Ms. Arline Bilbo
Member Services Manager
U.S. Pharmacopeial Convention, Inc.
1260 1 Twinbrook Parkway
Rockville, Maryland 30853

Dear Ms. Bilbo:

On behalf of the Food and Drug Administration, I am pleased to respond to the September 1, 1999, Member Memorandum from Dr. Edwin D. Bransome, Jr. requesting comments on the strategic planning process and the preliminary USP Strategic Plan. The final Strategic Plan will guide the development of annual operational plans for fiscal years 200 l-2003.

We believe this involvement of USP Convention members will help the Board of Trustees to develop a sound, well conceived strategic plan for USP activities as we enter the new millennium. The early request for input provides FDA with the opportunity to make our views available to the Board of Trustees as they finalize the plan. We recognize that the process has been well thought out and commend the Board for taking this step. The fact that the success of the strategic plan will be evaluated by Convention members, Committee of Revision members, and the Board leadership in 3003 is a welcome opportunity. We are especially encouraged that this process will consider the comments from the Committee of Revision members as the Committee is the heart of the USP process. It is through their dedication as volunteers that USP is the world's leading Pharmacopeia.

We have the following comments on specific items in the preliminary Strategic Plan:

Goal 1: Ensure the continued leadership of the U.S. Pharmacopeia (USP) and the National Formulary (NF)

1.1 The availability of the web-based version of USP-NF will increase its utilization not only by the U.S. pharmaceutical community but also by numerous countries around the world. This will help to provide additional funds for USP priority projects.

1.2 We fully support the Committee of Revision established New Monograph Development Policy. The goal of publishing proposed monographs for at least 90 percent of new approved drugs means that public standards will be available for those products of commerce in a timely manner.

1.3 The plan to establish and maintain general notices and chapters that are current with the state of the technology and the evolution of pharmaceutical science means that the end users of these notices and chapters will be assured that their drugs are of the highest quality possible.

1.4 The regulation of biotechnology-derived medicines and novel (customized) therapeutic modalities requires specialized expertise. We support USP in its efforts to develop monographs for the control of the identity, strength, quality, purity, and potency of these products.

1.5 We believe that neither FDA nor USP has enough experience with the regulation of dietary supplements to develop appropriate standards at this point. We would welcome the opportunity for further discussion with USP on this project.

I .6 While the NF currently contains monographs for most of the commonly used excipients, we are aware that novel excipients are being used more frequently by the pharmaceutical industry. FDA considers the inclusion of monographs for these materials an important factor in ensuring that appropriate public standards are available.

1.7 FDA will do whatever we can to help protect USP standards recognition from erosion through changes in regulatory policy, where appropriate.

1.8 In today's world of the multinational pharmaceutical industry, strong relationships with international health organizations is a must, not only for USP but also for FDA. We encourage USP to develop and maintain these relationships, and we hope to have the opportunity to work in concert with USP in the coming years.

1.9 Continued harmonization with the European and Japanese pharmacopoeias will help to further the goals of the International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals (ICI-I). As you are aware, FDA has been an active partner in the ICH efforts to develop harmonized guidelines on the safety, efficacy, and quality of new drug substances and new drug products that have not been

previously registered in the three ICH regions. In particular, pharmacopoeia1 harmonization is extremely important to the Q6A and Q6B guidelines dealing with setting of specifications for chemical substances and biotechnology substances, respectively.

1.10 Providing ready access to USP standards and reference standards for foreign governments and pharmaceutical industries will advance the quality of their drug supplies and the public health of their citizens, as well as the public health of our citizens if the products are marketed in the U.S.

1.11 Contributions by USP to the Expert Working Groups of the Veterinary ICH will have a similar impact to the contribution to the ICH Expert Working Groups. We encourage USP to be as proactive as possibie in this endeavor.

Goal 2: Improve availability of and access to USP Reference Standards

2.1 Ready access to USP Reference Standards is critical for both regulators and the pharmaceutical industry. FDA is proud to be a contributor to the laboratory evaluation program for proposed new and replacement lots of USP Reference Standards. We have long recognized the critical importance of maintaining the highest quality materials for quality control and regulatory purposes. We also realize that USP depends on the pharmaceutical industry as its source of reference standards and that, at times, those materials are not always forthcoming. FDA is willing to work with USP to ensure that there is an adequate supply of reference standards and to continue our joint role to improve the reference'standards program.

Goal 3: Maintain USP's leadership role in assuring the availability and use of evidence-based drug and therapeutic information.

3.1 We support the concept of determining and refining "value-added" information for the USP DI database so long as any off-label information does not erode the appropriate regulatory route of submission by applicants to demonstrate broader therapy claims.

3.2 As with 3.1, we are concerned about promoting "new and off-label" use in drug therapy decision making without the appropriate safeguards of well-controlled clinical trials.

Goal 4: Improve USP's recognition and standing in, and contributions to, the public, health professions, scientific, legislative and regulatory communities.

4.1 We strongly support the development of a Public Health Program designed to improve the health of and the appropriate use of medicines by patients and special populations. Strategies to increase patient compliance and communication with healthcare professionals will be of benefit to the public.

4.2 Improved communications among governmental, professional, and scientific organizations and USP is a noteworthy goal. Good communication is necessary to help USP achieve its missions and goals of standards setting, information development, and reporting and preventing medication errors.

4.3 As indicated above (3.2), we have some concern about the promotion of new and off-label use. However, anything that USP can do to improve the public comment and feedback processes is to be encouraged, as is the active participation in the establishment of compendia1 standards.

4.4 FDA supports the goal of increasing the use of USP and NF standards in pharmacy practice and pharmacy education.

Goal 5: Increase recognition of USP as the leader in medication error reporting and prevention.

5.1 We would be pleased to work with USP to ensure the continued maintenance of an accurate medication error reporting system. As you are aware, FDA has given the reduction of medication errors extremely high priority as evidenced by our MedWatch program. Our one concern is that the use of both the MedMARx system and MedWatch not lead to incomplete information in either system's database.

5.2 USP has our support for its efforts to adapt the MedMARx system to ambulatory care settings.

5.3 FDA supports extending the MedMARx system to non-US settings as a means of providing increased assurance that citizens in those countries will receive their intended medications.

Goal 6: Ensure USP's long-term financial viability.

6.1 FDA continues to support the maintenance of the USP Reference Standards program as indicated above. We consider the continued availability of high quality Reference Standards critical to our ability to maintain the quality of pharmaceuticals sold in the United States.

6.2 – 6.4 We support new USP initiatives that are in concert with FDA's mission to protect the public health.

Goal 7: Ensure the Committee of Revision is optimally organized and supported to meet the challenges of the 2000-2005 revision cycle.

7.1 The Ad Hoc Committee on the Structure and Processes of the Committee of Revision will have considerable influence in the implementation of the strategic plan by the Committee of Revision. FDA supports these efforts and looks forward to reports of progress in the years ahead.

7.2 We enthusiastically support the recruitment of highly qualified experts for the 2000-2005 Committee of Revision. We are especially pleased that a number of FDA scientists have indicated their interest in serving on this Committee.

7.3 The recruitment of qualified individuals for the USP DI value-added information development process also is considered an important endeavor, and we would hope that FDA scientists will be involved in this effort, as well.

7.4 FDA supports any efforts that will improve the efficiency of the work flow of Corm-nit-tee of Revision-work as this will lead to the publication of new and revised monographs in a shorter time frame and goes hand-in-hand with the efforts to publish monographs for recently approved drugs within a three year period.

7.5 We consider an effective orientation program for members of the new Committee of Revision, especially for new members, critical to the implementation of the USP strategic plan. FDA would be happy to work with USP on this program so that new members have a better understanding of the relationship between our two organizations.

Again, on behalf of the FDA, I thank you for the opportunity to comment on the strategic plan; we look forward to future interactions with the USP and the Committee of Revision.

Sincerely,

BA Schwetz

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of Food and Drugs