DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 95D–0349]

Immediate Release Solid Oral Dosage Forms; Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing; In Vivo Bioequivalence Documentation; Guidance

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is publishing a guidance entitled ''Immediate Release Solid Oral Dosage Forms; Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing; In Vivo Bioequivalence Documentation.'' The guidance sets forth application information that should be provided to the Center for Drug Evaluation and Research (CDER) to assure continuing product quality and performance characteristics of immediate release solid oral dose formulations for specified changes. The guidance fulfills a commitment made in the President's National Performance report, ''Reinventing Drug and Medical Device Regulations,'' April 1995, to reduce through guidance the number of manufacturing changes that require preapproval by FDA. The guidance provides recommendations to sponsors of new drug applications (NDA's), abbreviated antibiotic applications (AADA's), and abbreviated new drug applications (ANDA's) who intend, during the postapproval period, to change the components or composition of the drug, site of manufacture, scale-up/scale-down of manufacture, and/or manufacturing process or equipment. The guidance was prepared by the Immediate Release Scale-Up and Postapproval Change Expert Working Group of the Chemistry Manufacturing Controls Coordinating Committee (CMC CC) at CDER.

DATES: Written comments may be submitted at any time.

ADDRESSES: Submit written requests for single copies of the guidance ''Immediate Release Solid Oral Dosage Forms; Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing; In Vivo Bioequivalence Documentation'' to the Consumer Affairs Branch (HFD–8) (previously the CDER Executive Secretariat Staff), Center for Drug Evaluation and Research, Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855. Send two self-addressed adhesive labels to assist that office in processing your requests. An electronic version of the guidance document is also available via Internet. Requesting persons should connect to the CDER FTP server (CDVS2.CDER.FDA.GOV) using the FTP protocol. The guidance is available in WordPerfect Versions 5.2 and 6.0. Submit written comments on the guidance to the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857. Requests and comments should be identified with the docket number found in brackets in the heading of this document. A copy of the guidance and received comments are available for public examination in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

FOR FURTHER INFORMATION CONTACT: Allen Rudman, Center for Drug Evaluation and Research (HFD–645), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301–594–0375.

SUPPLEMENTARY INFORMATION: FDA is publishing a guidance entitled ''Immediate Release Solid Oral Dosage Forms; Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing; In Vivo Bioequivalence Documentation.'' The guidance specifies application information that sponsors should provide to CDER to assure continuing product quality and performance characteristics of immediate release solid oral dose formulations for changes made in NDA's, AADA's, and ANDA's. The guidance fulfills a commitment made in the President's National Performance report, ''Reinventing Drug and Medical Device Regulations,'' April 1995, to reduce through guidance the number of manufacturing changes that require preapproval by FDA.

The guidance is the result of: (1) A workshop on the scale-up of immediate release drug products conducted by the American Association of Pharmaceutical Scientists in conjunction with the United States Pharmacopoeial Convention and FDA; (2) research conducted by the University of Maryland at Baltimore on the chemistry, manufacturing, and controls of immediate release drug products under the FDA/University of Maryland Manufacturing Research Contract; (3) the drug categorization research conducted at the University of Michigan and the University of Uppsala on the permeability of drug substances; and (4) the Scale-Up and Post Approval Changes (SUPAC) Task Force which was established by the Center for Drug Evaluation and Research Chemistry, Manufacturing, and Controls Coordinating Committee to develop guidance on scale-up and other postapproval changes.

The guidance describes: (1) The levels of change that may be made in the components or composition of the drug, site of manufacture, scale-up/scale-down of manufacture, and manufacturing process and equipment; (2) the chemistry, manufacturing, and controls tests for each level of change; (3) in vitro dissolution tests and/or in vivo bioequivalence tests for each level of change; and (4) filing documentation.

The regulations in § 314.70(a) (21 CFR 314.70(a)) state that applicants may make changes to an approved application in accordance with a guideline, notice, or regulation published in the Federal Register that provides for a less burdensome notification of the change (for example, by notification at the time a supplement is submitted or in the next annual report). This guidance permits less burdensome notice of certain postapproval changes within the meaning of § 314.70(a).

For postapproval changes for immediate release dosage forms that affect components and composition, scale-up, site change, and manufacturing process or equipment changes, this guidance supersedes the recommendations in section 4.G of the Office of Generic Drugs Policy and Procedure Guide 22–90 (September 11, 1990). For all other dosage forms and changes, this guidance does not affect the recommendations in Guide 22–90.

This guidance is an informal communication under 21 CFR 10.90(b)(9) that reflects the best judgment of CDER employees at this time. It does not create or confer any rights, privileges, or benefits for or on behalf of any person, nor does it operate to bind or obligate FDA in any way. Different approaches may be followed, but the applicant is encouraged to discuss significant variations in advance with FDA review divisions to preclude spending time and effort in preparing a submission that FDA may later determine to be unacceptable.

Interested persons may, at any time, submit written comments on the guidance to the Dockets Management Branch (address above). Two copies of any comments are to be submitted, except that individuals may submit one

copy. Comments are to be identified with the docket number found in brackets in the heading of this document. The guidance and received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

The text of the guidance follows:

Immediate Release Solid Oral Dosage Forms; Scale-up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing; In Vivo Bioequivalence Documentation; Guidance

I. Purpose of Guidance

This guidance provides recommendations to sponsors of new drug applications (NDA's), abbreviated new drug applications (ANDA's), and abbreviated antibiotic applications (AADA's) who intend, during the postapproval period, to change: (1) The components or composition; (2) the site of manufacture; (3) the scale-up/scale-down of manufacture; and/or (4) the manufacturing (process and equipment) of an immediate release oral dosage formulation.

This guidance is the result of: (1) A workshop on the scale-up of immediate release drug products conducted by the American Association of Pharmaceutical Scientists in conjunction with the United States Pharmacopoeial Convention and the Food and Drug Administration (FDA); (2) research conducted by the University of Maryland at Baltimore on the chemistry, manufacturing, and controls of immediate release drug products under the FDA/University of Maryland Manufacturing Research Contract; (3) the drug categorization research conducted at the University of Michigan and the University of Uppsala on the permeability of drug substances; and (4) the Scale-Up and Post Approval Changes (SUPAC) Task Force which was established by the Center for Drug Evaluation and Research (CDER) Chemistry, Manufacturing, and Controls Coordinating Committee to develop guidance on scale-up and other postapproval changes.

The guidance defines: (1) Levels of change; (2) recommended chemistry, manufacturing, and controls tests for each level of change; (3) in vitro dissolution tests and/or in vivo bioequivalence tests for each level of change; and (4) documentation that should support the change. For those changes filed in a ''changes being effected supplement'' (§ 314.70(c) (21 CFR 314.70(c))), FDA may, after a review of the supplemental information, decide that the changes are not approvable. This guidance thus sets forth application information that should be provided to CDER to assure continuing product quality and performance characteristics of an immediate release solid oral dose formulation for specified postapproval changes. This guidance does not comment on or otherwise affect compliance/inspection documentation that has been defined by CDER's Office of Compliance or FDA's Office of Regulatory Affairs. This guidance does not affect any postapproval changes other than the ones specified. For changes not addressed in this guidance, or for multiple changes submitted at one time or over a short period of time, or where the number of batches recommended for stability testing is not specified, sponsors should contact the appropriate CDER review division or consult other CDER guidances/guidelines to obtain information about tests and application documentation.

The regulations in § 314.70(a) state that applicants may make changes to an approved application in accordance with a guideline, notice, or regulation published in the Federal Register that provides for a less burdensome notification of the change (for example, by notification at the time a supplement is submitted or in the next annual report). This guidance permits less burdensome notice of certain postapproval changes within the meaning of § 314.70(a).

For postapproval changes for immediate release dosage forms that affect components and composition, scale-up, site change, and manufacturing process or equipment changes, this guidance supersedes the recommendations in section 4.G of the Office of Generic Drugs Policy and Procedure Guide 22–90 (September 11, 1990). For all other dosage forms and changes, this guidance does not affect the recommendations in Guide 22–90.

II. Definition of Terms [1]

A. Batch

A specific quantity of a drug or other material produced according to a single manufacturing order during the same cycle of manufacture and intended to have uniform character and quality, within specified limits (21 CFR 210.3(b)(2)).

B. Contiguous campus

Continuous or unbroken site or a set of buildings in adjacent city blocks.

C. Dissolution testing

Case A: Dissolution of Q = 85 percent in 15 minutes in 900 milliliters (mL) of 0.1*N* hydrochloride (HCl), using the United States Pharmacopeia (U.S.P.) <711> Apparatus 1 at 100 revolutions per minute (rpm) or Apparatus 2 at 50 rpm.

Case B: Multi-point dissolution profile in the application/compendial medium at 15, 30, 45, 60, and 120 minutes or until an asymptote is reached for the proposed and currently accepted formulation.

Case C: Multi-point dissolution profiles performed in water, 0.1*N* HCl, and U.S.P. buffer media at pH 4.5, 6.5, and 7.5 (five separate profiles) for the proposed and currently accepted formulations. Adequate sampling should be performed at 15, 30, 45, 60, and 120 minutes until either 90 percent of drug from the drug product is dissolved or an asymptote is reached. A surfactant may be used with appropriate justification.

D. Drug product

A drug product is a finished dosage form (e.g., tablet, capsule, or solution) that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients (21 CFR 314.3(b)). A solid oral dosage form includes tablets, chewable tablets, capsules, and soft gelatin capsules.

E. Drug substance

An active ingredient 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 of any function of the human body, but does not include intermediates used in the synthesis of such ingredient (21 CFR 314.3(b)).

F. Equipment

Automated or non-automated, mechanical or non-mechanical equipment used to produce the drug product, including equipment used to package the drug product.

G. Formulation

A listing of the ingredients and composition of the dosage form.

H. Justification

Reports containing scientific data and expert professional judgment to substantiate decisions.

I. New drug substance

Any substance that, when used in the manufacture, processing, or packing of a drug, causes that drug to be a new drug, but does not include intermediates used in the synthesis of such substance (21 CFR 310.3(g)).

J. Operating principle

Rules or concepts governing the operation of the system.

K. Pilot scale

The manufacture of either drug substance or drug product by a procedure fully representative of and simulating that used for full manufacturing scale.

For solid oral dosage forms, this is generally taken to be, at a minimum, one-tenth that of full production, or 100,000 tablets or capsules, whichever is larger (see the Federal Register of September 22, 1994, 59 FR 48754–48759).

L. Process

A series of operations and/or actions used to produce a desired result.

M. Ranges

The extent to which or the limits between which acceptable variation exists.

N. Same

Agreeing in kind, amount; unchanged in character or condition.

O. Scale-up

The process of increasing the batch size.

P. Scale-down

The process of decreasing the batch size.

Q. Similar

Having a general likeness.

[1] See Workshop Report: Skelly, et al., ''Scale-up of Immediate Release Oral Solid Dosage Forms,'' *Pharmaceutical Research*, 10(2):313–316; and the Federal Register of September 22, 1994, 59 FR 48754–59.

R. Significant body of information

A significant body of information on the stability of the drug product is likely to exist after 5 years of commercial experience for new molecular entities, or 3 years of commercial experience for new dosage forms.

S. Validation

Establishing through documented evidence a high degree of assurance that a specific process will consistently produce a product that meets its predetermined specifications and quality attributes. A validated manufacturing process is one that has been proven to do what it purports or is represented to do. The proof of validation is obtained through collection and evaluation of data, preferably beginning from the process development phase and continuing through into the production phase. Validation necessarily includes process qualification (the qualification of materials, equipment, systems, buildings, and personnel), but it also includes the control of the entire processes for repeated batches or runs.

III. Components and Composition

This section of the guidance focuses on changes in excipients in the drug product. Changes in the amount of drug substance are not addressed by this guidance. Changes in components or composition that have the effect of adding a new excipient or deleting an excipient are defined at Level 3 (defined below), except as described below.

A. Level 1 Changes

1. Definition of Level

Level 1 changes are those that are unlikely to have any detectable impact on formulation quality and performance.

Examples:

a. Deletion or partial deletion of an ingredient intended to affect the color or flavor of the drug product; or change in the ingredient of the printing ink to another approved ingredient.

b. Changes in excipients, expressed as percentage (w/w) of total formulation, less than or equal to the following percent ranges:

EXCIPIENT	PERCENT EXCIPIENT (w/w) OUT OF TOTAL TARGET DOSAGE FORM WEIGHT
Filler	±5
Disintegrant	
Starch	±3
Other	±1
Binder	±0.5
Lubricant	
Calcium (Ca) or Magnesium (Mg) Stearate	±0.25
Other	±1
Glidant	
Talc	±1
Other	±0.1
Film Coat	±1

These percentages are based on the assumption that the drug substance in the drug product is formulated to 100% of label/potency. The total additive effect of all excipient changes should not be more than 5 percent. (Example: In a product consisting of active ingredient A, lactose, microcrystalline cellulose, and magnesium stearate, the lactose and microcrystalline cellulose should not vary by more than an absolute total of 5 percent (e.g., lactose increases 2.5 percent and microcrystalline cellulose decreases by 2.5 percent) relative to the target dosage form weight if it is to stay within the Level 1 range).

The components (active and excipients) in the formulation should have numerical targets that represent the nominal composition of the drug product on which any future changes in the composition of the product are to be based. Allowable changes in the composition should be based on the approved target composition and not on previous Level 1 changes in the composition.

2. Test Documentation

a. Chemistry Documentation

Application/compendial release requirements and stability testing.

Stability testing: One batch on long-term stability data reported in annual report.

b. Dissolution Documentation

None beyond application/compendial requirements.

c. In Vivo Bioequivalence Documentation

None.

3. Filing Documentation

Annual report (all information including long-term stability data).

B. Level 2 Changes

1. Definition of Level

Level 2 changes are those that could have a significant impact on formulation quality and performance. Tests and filing documentation for a Level 2 change vary depending on three factors: Therapeutic range, solubility, and permeability. Therapeutic range is defined as either narrow or non-narrow. A list of narrow therapeutic range drugs is provided in Appendix A. Drug solubility and drug permeability are defined as either low or high. Solubility is calculated based on the minimum concentration of drug (milligram (mg)/mL), in the largest dosage strength, determined in the physiological pH range (pH 1 to 8) and temperature (37±0.5°C). High solubility drugs are those with a dose/solubility volume of less than or equal to 250 mL. (Example: Compound A has as its lowest solubility at 37±0.5 °C, 1.0 mg/mL at pH 7, and is available in 100 mg, 200 mg, and 400 mg strengths. This drug would be considered a low solubility drug as its dose/solubility volume is greater than 250 mL (400 mg/1.0 mg/mL=400 mL). Permeability (P_e, centimeter per second) is defined as the effective human jejunal wall permeability of a drug and includes an apparent resistance to mass transport to the intestinal membrane. High permeability drugs are generally those with an extent of absorption greater than 90 percent in the absence of documented instability in the gastrointestinal tract, or those whose permeability attributes have been determined experimentally.

Examples:

a. Change in the technical grade of an excipient. (Example: Avicel PH102 versus Avicel PH200.)

b. Changes in excipients, expressed as percent (w/w) of total formulation, greater than those listed above for a Level 1 change but less than or equal to the following percent ranges (which represent a twofold increase over Level 1 changes):

EXCIPIENT	PERCENT EXCIPIENT (w/w) OUT OF TOTAL TARGET DOSAGE FORM WEIGHT
Filler	±10
Disintegrant	
Starch	±6
Other	±2
Binder	±1
Lubricant	
Ca or Mg Stearate	±0.5
Other	±2
Glidant	
Talc	±2
Other	±0.2
Film Coat	±2

These percentages are based on the assumption that the drug substance in the drug product is formulated to 100 percent of label/potency. The total additive effect of all excipient changes should not change by more than 10 percent.

The components (active and excipients) in the formulation should have numerical targets that represent the nominal composition of the drug product on which any future changes in the composition of the product are to be based. Allowable changes in the composition should be based on the approved target composition and not on the composition based on previous Level 1 or Level 2 changes.

2. Test Documentation

a. Chemistry Documentation

Application/compendial release requirements and batch records.

Stability testing: One batch with 3 months accelerated stability data in supplement and 1 batch on long-term stability.

b. Dissolution Documentation

Case A: High Permeability, High Solubility Drugs

Dissolution of 85 percent in 15 minutes in 900 mL of 0.1*N* HCl. If a drug product fails to meet this description, the applicant should perform the tests described for Case B or Case C (below).

Case B: Low Permeability, High Solubility Drugs

Multi-point dissolution profile should be performed in the application/compendial medium at 15, 30, 45, 60, and 120 minutes or until an asymptote is reached. The dissolution profile of the proposed and currently used drug product formulations should be similar.

Case C: High Permeability, Low Solubility Drugs

Multi-point dissolution profiles should be performed in water, 0.1*N* HCl, and U.S.P. buffer media at pH 4.5, 6.5, and 7.5 (five separate profiles) for the proposed and currently accepted formulations. Adequate sampling should be performed at 15, 30, 45, 60, and 120 minutes until either 90 percent of drug from the drug product is dissolved or an asymptote is reached. A surfactant may be used, but only with appropriate justification. The dissolution profile of the proposed and currently used drug product formulations should be similar.

c. In Vivo Bioequivalence Documentation

None: if the situation does not meet the description in Case A, Case B, or Case C, refer to Level 3 changes.

3. Filing Documentation

Prior approval supplement (all information including accelerated stability data); annual report (long-term stability data).

C. Level 3 Changes

1. Definition of Level

Level 3 changes are those that are likely to have a significant impact on formulation quality and performance. Tests and filing documentation vary depending on the following three factors: Therapeutic range, solubility, and permeability.

Examples:

a. Any qualitative and quantitative excipient changes to a narrow therapeutic drug beyond the ranges noted in Section III.A.1.b.

b. All other drugs not meeting the dissolution cases under Section III.B.2.b.

c. Changes in the excipient ranges of low solubility, low permeability drugs beyond those listed in Section III.A.1.b.

d. Changes in the excipient ranges of all drugs beyond those listed in Section III.B.1.b.

2. Test Documentation

a. Chemistry Documentation

Application/compendial release requirements and batch records.

Significant body of information available:

One batch with 3 months accelerated stability data reported in supplement; one batch on long-term stability data reported in annual report.

Significant body of information not available:

Up to three batches with 3 months accelerated stability data reported in supplement; up to three batches on long-term stability data reported in annual report.

b. Dissolution Documentation

Case B dissolution profile as described in Section III.B.2.b.

c. In Vivo Bioequivalence Documentation

Full bioequivalence study. The bioequivalence study may be waived when an acceptable in vivo/in vitro correlation has been verified.

3. Filing Documentation

Prior approval supplement (all information including accelerated stability data); annual report (long-term stability data).

IV. Site Changes

Site changes consist of changes in location of the site of manufacture for both company-owned and contract manufacturing facilities and do not include any scale-up changes, changes in manufacturing (including process and/or equipment), or changes in components or composition. Scale-up is addressed in Section V of this guidance. New manufacturing locations should have a satisfactory current good manufacturing practice (CGMP) inspection.

A. Level 1 Changes

1. Definition of Level

Level 1 changes consist of site changes within a single facility where the same equipment, standard operating procedures (SOP's), environmental conditions (e.g., temperature and humidity) and controls, and personnel common to both manufacturing sites are used, and where no changes are made to the manufacturing batch records, except for administrative information and the location of the facility. Common is defined as employees already working on the campus who have suitable experience with the manufacturing process.

2. Test Documentation

a. Chemistry Documentation

None beyond application/compendial release requirements.

b. Dissolution Documentation

None beyond application/compendial release requirements.

c. In Vivo Bioequivalence Documentation

None.

3. Filing Documentation

Annual report.

B. Level 2 Changes

1. Definition of Level

Level 2 changes consist of site changes within a contiguous campus, or between facilities in adjacent city blocks, where the same equipment, SOP's, environmental conditions (e.g., temperature and humidity) and controls, and personnel common to both manufacturing sites are used, and where no changes are made to the manufacturing batch records, except for administrative information and the location of the facility.

2. Test Documentation

a. Chemistry Documentation

Location of new site and updated batch records. None beyond application/compendial release requirements.

One batch on long-term stability data reported in annual report.

b. Dissolution Documentation

None beyond application/compendial release requirements.

c. In Vivo Bioequivalence Documentation

None.

3. Filing Documentation

Changes being effected supplement; annual report (long-term stability test data).

C. Level 3 Changes

1. Definition of Level

Level 3 changes consist of a change in manufacturing site to a different campus. A different campus is defined as one that is not on the same original contiguous site or where the facilities are not in adjacent city blocks. To qualify as a Level 3 change, the same equipment, SOP's, environmental conditions, and controls should be used in the manufacturing process at the new site, and no changes may be made to the manufacturing batch records except for administrative information, location, and language translation, where needed.

2. Test Documentation

a. Chemistry Documentation

Location of new site and updated batch records.

Application/compendial release requirements.

Stability:

Significant body of information available:

One batch with 3 months accelerated stability data reported in supplement; one batch on long-term stability data reported in annual report.

Significant body of information not available:

Up to three batches with 3 months accelerated stability data reported in supplement; up to three batches on long-term stability data reported in annual report.

b. Dissolution Documentation

Case B: Multi-point dissolution profile should be performed in the application/compendial medium at 15, 30, 45, 60, and 120 minutes or until an asymptote is reached. The dissolution profile of the drug product at the current and proposed site should be similar.

c. In Vivo Bioequivalence Documentation

None.

3. Filing Documentation

Changes being effected supplement; annual report (long-term stability data).

V. Changes in Batch Size (Scale-Up/Scale-Down)

Postapproval changes in the size of a batch from the pivotal/pilot scale biobatch material to larger or smaller production batches call for submission of additional information in the application. Scale-down below 100,000 dosage units is not covered by this guidance. All scale-up changes should be properly validated and, where needed, inspected by appropriate agency personnel.

A. Level 1 Changes

1. Definition of Level

Change in batch size, up to and including a factor of 10 times the size of the pilot/biobatch, where: (1) The equipment used to produce the test batch(es) is of the same design and operating principles; (2) the batch(es) is (are) manufactured in full compliance with CGMP's; and (3) the same SOP's and controls, as well as the same formulation and manufacturing procedures, are used on the test batch(es) and on the full-scale production batch(es).

2. Test Documentation

a. Chemistry Documentation

Application/compendial release requirements. Notification of change and submission of updated batch records in annual report.

One batch on long-term stability reported in annual report.

b. Dissolution Documentation

None beyond application/compendial release requirements.

c. In Vivo Bioequivalence
None.

3. Filing Documentation

Annual report (long-term stability data).

B. Level 2 Changes

1. Definition of Level

Changes in batch size beyond a factor of 10 times the size of the pilot/biobatch, where: (1) The equipment used to produce the test batch(es) is of the same design and operating principles; (2) the batch(es) is (are) manufactured in full compliance with CGMP'S; and (3) the same SOP's and controls as well as the same formulation and manufacturing procedures are used on the test batch(es) and on the full-scale production batch(es).

2. Test Documentation

a. Chemistry Documentation
Application/compendial release requirements. Notification of change and submission of updated batch records.
Stability testing: One batch with 3 months accelerated stability data and one batch on long-term stability.
b. Dissolution Documentation
Case B testing.
c. In Vivo Bioequivalence
None.
3. Filing Documentation
Changes being effected supplement; annual report (long-term stability data).

VI. Manufacturing

Manufacturing changes may affect both equipment used in the manufacturing process and the process itself.

A. Equipment

1. *Level 1 Changes*

a. Definition of Change
This category consists of: (1) Change from nonautomated or nonmechanical equipment to automated or mechanical equipment to move ingredients; and (2) change to alternative equipment of the same design and operating principles of the same or of a different capacity.
b. Test Documentation
i. Chemistry Documentation
Application/compendial release requirements. Notification of change and submission of updated batch records.
Stability testing: One batch on long-term stability.
ii. Dissolution Documentation
None beyond application/compendial release requirements.
iii. In Vivo Bioequivalence Documentation
None.
c. Filing Documentation
Annual report (long-term stability data).

2. *Level 2 Changes*

a. Definition of Level
Change in equipment to a different design and different operating principles.
b. Test Documentation
i. Chemistry Documentation
Application/compendial release requirements. Notification of change and submission of updated batch records.
Stability testing:
Significant body of information available:
One batch with 3 months accelerated stability data reported in supplement; one batch on long-term stability data reported in annual report.
Significant body of information not available:
Up to three batches with 3 months accelerated stability data reported in supplement; up to three batches on long-term stability data reported in annual report.
ii. Dissolution Documentation
Case C dissolution profile.
iii. In Vivo Bioequivalence Documentation
None.
c. Filing Documentation
Prior approval supplement with justification for change; annual report (long-term stability data).

B. Process

1. Level 1 Change

a. Definition of Level
This category includes process changes including changes such as mixing times and operating speeds within application/validation ranges.
b. Test Documentation
i. Chemistry Documentation
None beyond application/compendial release requirements.
ii. Dissolution Documentation
None beyond application/compendial release requirements.
iii. In Vivo Bioequivalence Documentation
None.
c. Filing Documentation
Annual report.

2. *Level 2 Changes*

a. Definition of Level
This category includes process changes, including changes such as mixing times and operating speeds outside of application/validation ranges.
b. Test Documentation
i. Chemistry Documentation
Application/compendial release requirements. Notification of change and submission of updated batch records.
Stability testing: One batch on long-term stability.
ii. Dissolution Documentation
Case B dissolution profile.
iii. In Vivo Bioequivalence Documentation
None.
c. Filing Documentation
Changes being effected supplement; annual report (long-term stability data).

3. *Level 3 Changes*

a. Definition of Level
This category includes change in the type of process used in the manufacture of the drug product, such as a change from wet granulation to direct compression of dry powder.
b. Test Documentation
i. Chemistry Documentation
Application/compendial release requirements. Notification of change and submission of updated batch records.
Stability testing:
Significant body of information available:
One batch with 3 months accelerated stability data reported in supplement; one batch on long-term stability data reported in annual report.
Significant body of information not available:
Up to three batches with 3 months accelerated stability data reported in supplement; up to three batches on long-term stability data reported in annual report.
ii. Dissolution Documentation
Case B dissolution.
iii. In Vivo Bioequivalence Documentation
In vivo bioequivalence study. The bioequivalence study may be waived if a suitable in vivo/in vitro correlation has been verified.
c. Filing Documentation
Prior approval supplement with justification; annual report (long-term stability data).

VII. In Vitro Dissolution

See current United States Pharmacopeia/National Formulary, section <711>, for general dissolution specifications. All profiles should be conducted on at least 12 individual dosage units.
Dissolution profiles may be compared using the following equation that defines a similarity factor (f_2):
$f_2 = 50 \text{ LOG } \{[1+1/n \sum^{n}_{t=1} (R_t-T_t)^2]^{-0.5} \text{ x } 100\}$
where R_t and T_t are the percent dissolved at each time point. An f_2 value between 50 and 100 suggests the two dissolution profiles are similar.

VIII. In Vivo Bioequivalence Studies

Below is a general outline of an in vivo bioequivalence study. It is intended as a guide and the design of the actual study may vary depending on the drug and dosage form.

A. Objective:

To compare the rate and extent of absorption of the drug product for which the manufacture has been changed, as defined in this guidance, to the drug product manufactured before the change.

B. Design:

The study design should be a single dose, two-treatment, two-period crossover with adequate washout period between the two phases of the study. Equal numbers of subjects should be randomly assigned to each of the two dosing sequences.

C. Selection of Subjects:

The number of subjects enrolled in the bioequivalence study should be determined statistically to account for the intrasubject variability and to meet the current bioequivalence interval.

D. Procedure:

Each subject should receive the following two treatments:
Treatment 1: Drug product manufactured with the proposed change.
Treatment 2: Drug product manufactured prior to the proposed change.
Following an overnight fast of at least 10 hours, subjects should receive either Treatments 1 or 2 with 240 mL water. Food should not be allowed until 4 hours after dosing. Water may be allowed after the first hour. Subjects should be served standardized meals beginning at 4 hours during the study.

E. Restrictions:

Before and during each study phase, water may be allowed *ad libitum* except for 1 hour before and after drug administration. The subject should be served standardized meals and beverages at specified times. No alcohol or xanthine- or caffeine-containing foods and beverages should be consumed for 48 hours before each study period and until after the last blood sample is collected.

F. Blood Sampling:

Blood samples should be collected in sufficient volume for analysis of parent drug and active metabolite(s), if any. The sampling times should be such that it should be able to capture the C_{max} and T_{max} during the absorption period. Sampling should be carried out for at least three terminal elimination half-lives for both parent drug and active metabolite(s). Whole blood, plasma, or serum, whichever is appropriate for the analytes, should be harvested promptly and samples should be frozen at -20 °C or -70 °C to maintain sample stability.

G. Analytical Method:

The assay methodology selected should ensure specificity, accuracy, interday and intraday precision, linearity of standard curves, and adequate sensitivity, recovery, and stability of the samples under the storage and handling conditions associated with the analytical method.

H. Pharmacokinetic Analysis:

From the plasma drug concentration-time data, AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, K_{e1} and $t_{1/2}$ should be estimated.

I. Statistical Analysis:

Analysis of variance appropriate for a crossover design on the pharmacokinetic parameters using the general linear models procedures of SAS or an equivalent program should be performed, with examination of period, sequence, and treatment effects. The 90 percent confidence intervals for the estimates of the difference between the test and reference least squares means for the pharmacokinetic parameters (AUC_{0-t}, AUC_{0-inf}, Cmax) should be calculated, using the two one-sided t-test procedure.

Appendix A

Narrow Therapeutic Range Drugs

Aminophylline Tablets, ER Tablets
Carbamazepine Tablets, Oral Suspension
Clindamycin Hydrochloride Capsules
Clonidine Hydrochloride Tablets
Clonidine Transdermal Patches
Dyphylline Tablets
Disopyramide Phosphate Capsules, ER Capsules
Ethinyl Estradiol/Progestin Oral Contraceptive Tablets
Guanethidine Sulfate Tablets
Isoetharine Mesylate Inhalation Aerosol
Isoproterenol Sulfate Tablets
Lithium Carbonate Capsules, Tablets, ER Tablets
Metaproterenol Sulfate Tablets
Minoxidil Tablets
Oxtriphylline Tablets, DR Tablets, ER Tablets
Phenytoin, Sodium Capsules (Prompt or Extended), Oral Suspension
Prazosin Hydrochloride Capsules
Primidone Tablets, Oral Suspension
Procainamide Hydrochloride, Capsules, Tablets, ER Tablets
Quinidine Sulfate Capsules, Tablets, ER Tablets
Quinidine Gluconate Tablets, ER Tablets
Theophylline Capsules, ER Capsules, Tablets, ER Tablets
Valproic Acid Capsules, Syrup
Divalproex, Sodium DR Capsules, DR Tablets
Warfarin, Sodium Tablets
ER - Extended Release
DR - Delayed Release

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William B. Schultz,

Deputy Commissioner for Policy.

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