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.