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.