

SCALE UP AND POSTAPPROVAL CHANGES (SUPAC) GUIDANCE FOR INDUSTRY: A REGULATORY NOTE

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REVIEW ARTICLE

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ABSTRACT

In today scenario, as per market demand there is definitely carry out an increment or decrease in production, this is called SUPAC. Different guidelines are provided for those different types of SUPAC in by different regulatory authority for manufacturing of product. Here SUPAC guidelines for USFDA are elaborated for production in this review article.

Keywords: SUPAC-Guideline for site changes, batch size, manufacturing, *in-vitro* dissolution, *in-vivo* bioequivalence, compendia, Biobatch, SUPAC Regulations.

INTRODUCTION

Technology transfer of a pharmaceutical product from research to the production floor with simultaneous increase in production outputs is commonly known as scale - up. In simple terms, the process of increasing batch size is termed as scale- up. Conversely, scale- down refers to decrease in batch size in response to reduced market requirements. (1)

Definition: The scale-up process and the changes made after approval in the composition, manufacturing process, manufacturing equipment, and change of site have become known as Scale-Up and Post approval Changes, or SUPAC. Changes are being made in the manufacturing process and chemistry of a drug product following approval and continue throughout its life. Depending upon foreseen (or unforeseen) requirements, there can be changes in the raw materials, process, equipment or manufacturing site, and batch size which ultimately affect quality attributes of a drug or finished product. Therefore, there is a need to anticipate and fully evaluate the impact of any kind of change on the quality of a drug or finished product. The intensity of the adverse

effect produced by a particular change depends on the type of dosage form.

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 post approval period, to change (2):

- 1) The components or composition
- 2) The site of manufacture
- 3) The scale-up/scale-down of manufacture
- 4) The manufacturing (process and equipment) of an immediate release oral formulation.

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

4) Documentation that should support the change. For those changes filed in a “changes being effected supplement” [21 CFR 314.70 (c)], the 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 post approval changes.

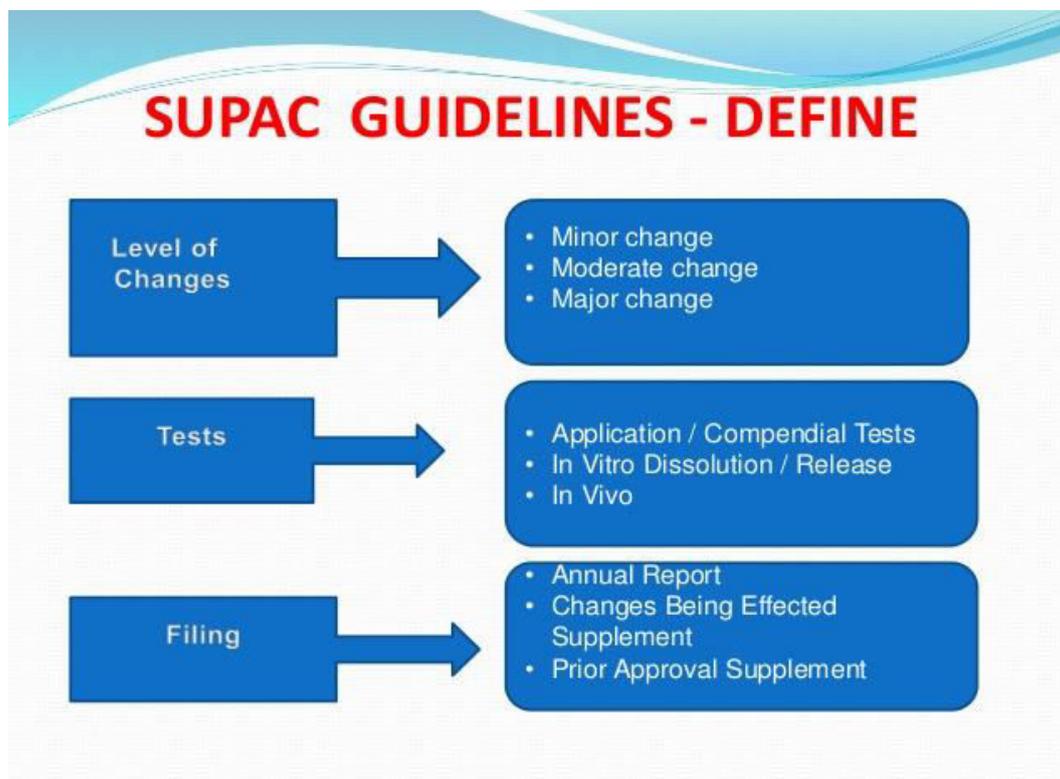


Figure: 1: SUPAC Guidelines

I. 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. (3)

A. Level 1 Changes

Definition: 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.

Test Documentation

- Chemistry Documentation: None beyond application/compendial release requirements.
- Dissolution Documentation: None beyond application/compendial release requirements.
- In Vivo Bioequivalence Documentation-None.

Filing Documentation-Annual report.

B. Level 2 Changes

Definition: 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.

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.

Filing Documentation

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

C. Level 3 Changes

Definition: 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.

Test Documentation

- Chemistry Documentation Location of new site and updated batch records. Application/ compendial release requirements. Stability: Significant body of data available: One batch with three months accelerated stability data reported in supplement; one batch on long-term stability data reported in annual report. Significant body of data not available: Up to three batches with three months accelerated stability data reported in

supplement; up to three batches on long-term stability data reported in annual report.

- Dissolution Documentation Case B: Multi-point dissolution profile should be performed in the application/compendia 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.
- In Vivo Bioequivalence Documentation-None.

Filing Documentation

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

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

Post-approval 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

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 is of the same design and operating principles;
- 2) The batch is manufactured in full compliance with CGMP's;
- 3) The same standard operating procedures (SOP's) and controls, as well as the same formulation and manufacturing procedures, are used on the test batch and on the full-scale production batch.

Test Documentation

- 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.

- Dissolution Documentation None beyond application/compendial release requirements.
- 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 ten times the size of the pilot/biobatch, where:

- 1) The equipment used to produce the test batch is of the same design and operating principles;
- 2) The batch is 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 and on the full-scale production batch.

2. Test Documentation

a. Chemistry Documentation Application/compendial release requirements. Notification of change and submission of updated batch records. Stability testing: One batch with three 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).

III. Manufacturing

Manufacturing changes may affect both equipment used in the manufacturing process and the process itself. (4)

A. Equipment 1. Level 1 Changes

a. Definition of Change This category consists of:

- 1) Change from non-automated or non-mechanical 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 data available: One batch with three months accelerated stability data reported in supplement; one batch on long-term stability data reported in annual report. Significant body of data not available: Up to three batches with three 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 Changes

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 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

data available: One batch with three months accelerated stability data reported in supplement; one batch on long-term stability data reported in annual report. Significant body of data not available: Up to three batches with three 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).

IV. 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): $f_2 = 50 \text{ LOG } \left\{ \left[\frac{1 + 1/n}{R - T} \right] \times 100 \right\}^{n - 0.5}$ 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.

V. 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. (5-7)

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 prior to 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: Product manufactured with the proposed change.

Treatment 2: Product manufactured prior to the proposed change.

Following an overnight fast of at least 10 hours, subjects should receive either Treatments 1 or 2 above 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: Prior to 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 prior to 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} , $AUC_{0-\infty}$, C_{max} , T_{max} , K_{el} 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% confidence intervals for the estimates of the difference between the test and reference least squares means for the pharmacokinetic parameters (AUC_{0-t} , $AUC_{0-\infty}$, C_{max} , T_{max}) should be calculated, using the two one-sided t-test procedure.

CONCLUSION

SUPAC-Industry Perspective: it is based on interview with six companies in first half of 1997 & concluded that SUPAC guide line have advantages that: Shorter waiting time for site transfers, reducing operating overhead & maintenance expenses. More rapid implementation of process and equipment changes, improved yield & Reduce failure investigations. More rapid implementation of batch size increases Production of fewer unmarketable stability batches. Reduce stability testing/costs.

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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