



Centurion
UNIVERSITY

**SCALE UP PROCESS
APPROVAL
CHANGES &
POST MARKETING
SURVEILLANCE**

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SCALE UP PROCESS APPROVAL CHANGES

INTRODUCTION:

- ❖ Technology transfer of 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 requirement.

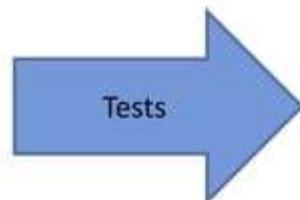
DEFINATION:

- ❖ 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.

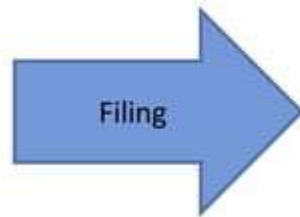
SUPAC GUIDELINES- DEFINE



- Minor change
- Moderate change
- Major change



- Application/Compendial Tests
- In Vitro Dissolution/Release
- In Vivo



- Annual Report
- Changes Being Effected Supplement
- Prior Approval Supplement

PURPOSE OF GUIDANCE:

- This guidance provides recommendations to sponsors of new drug applications (NDA), abbreviated new drug applications (ANDA), and abbreviated antibiotic application (AADA) who intend, during the post approval period, to change:
 - The components or composition
 - The site of manufacture
 - The scale-up/scale-down of manufacture
 - The manufacturing (process and equipment) of an immediate release oral formulations.

THE GUIDANCE DEFINES:

- Level of change
- Recommended chemistry, manufacturing, and controls tests for each level of change
- In-Vitro dissolution tests and/or in vivo bioequivalence tests for each level of change
- Documentation that should support the change. For those changes filed in a “changes being affected supplement”.

CURRENT REQUIREMENTS FOR POST-APPROVAL CHANGES

o I. Components/Composition:

In general, changes to the qualitative/quantitative composition of the formulation are considered major changes. Such changes require a Prior Approval Supplement unless otherwise exempted by regulation or guidance documents. The current guidance for industry, Changes to an Approved ANDA or NDA, does not address components/composition in detail; therefore, the SUPAC guidance remains in effect for defining components and composition changes and their reporting category thereof.

The addition or deletion of an ingredient can have an adverse effect on the dissolution profile of the finished product and on the in vivo bioequivalence to the reference listed drug. In general, any addition or deletion of an ingredient must be filed as a Prior Approval Supplement. The exception to this applies to colors, which can be removed or reduced from the formulation and filed in an annual report. Only in certain circumstances can changes to the components/composition be made with a less stringent reporting category.

TABLE 1 Components/Composition Change

Level	Definition	Category and example	Test documentation	Filing documentation
1 (Minor changes)	Changes unlikely to have any detectable impact on formulation quality and performance	<ul style="list-style-type: none"> i. Deletion/partial deletion of color or flavor or change in the ingredient of the printing ink ii. Changes in excipient (% w/w) of total for mulation not greater than 5% 	<ul style="list-style-type: none"> i. <i>Chemistry</i>: Compendial release and stability testing Stability: Long-term stability testing on one batch in annual report ii. <i>Dissolution</i>: None beyond application/ compendial requirement iii. <i>In vivo BE</i>: None 	Annual Report (all information including long-term stability data)
2 (Moderate changes)	Changes could have significant impact on formulation quality and performance as a result of change in therapeutic range, solubility, and permeability (low or high)	Changes in technical grade of an excipient or changes in excipient amount greater than expressed in level 1, but total additive effect of all excipients should not be greater than 10%	<ul style="list-style-type: none"> i. <i>Chemistry</i>: Compendial release, batch record Stability: one batch with 3 months' accelerated stability data in supplement and one batch on long-term stability ii. <i>Dissolution</i>: Using case A, B, and C as described in the guidance iii. <i>In Vivo BE</i>: None if situation does not meet above dissolution description 	Changes Being Effected (CBE) Supplement with long-term stability data

3 (Major changes)

Changes likely to have a significant impact on formulation quality and performance as a result of change in therapeutic range, solubility, and permeability (low or high)

- i. Qualitative and quantitative changes to a narrow therapeutic drug beyond the ranges of excipients noted in level 1
 - ii. High solubility and permeability drug, low permeability and high solubility drug and high permeability and low solubility drugs not meeting the dissolution criteria as stipulated in the guidance
 - iii. Changes in the excipient ranges of low solubility, low permeability drugs listed under level 1
- i. *Chemistry*: Compendial release and batch records
Stability: (a) 3 months' accelerated stability testing on one batch in supplement and long-term stability data on one batch in Annual Report if significant body of information is available; **(b)** 3 months' accelerated (supplement) and long-term stability (Annual Report) on up to three batches
 - ii. *Dissolution*: Multi-point dissolution profile in compendial medium at 15, 30, 45, 60, and 120 min or until asymptote is reached
 - iii. *In Vivo BE*: Full BE study except for the cases when in vitro/in vivo correlation is established

Prior Approval Supplement on all information including accelerated stability and long-term stability in Annual Report

II. Site Changes:

Site changes consists 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.

- **A. Level 1 Changes:**

- Level 1 changes consists 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.

- **B. Level 2 Changes:**

- Level 2 changes consists 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.

TABLE 2 Site Change

Level	Definition	Test documentation	Filing documentation
1 (Minor changes)	Site change within facility and using same equipment, SOPs, environment conditions (temperature and humidity), and controls, no changes made in manufacturing batch records	i. <i>Chemistry</i> : Compendial release ii. <i>Dissolution</i> : Compendial release iii. <i>In-vivo BE</i> : None	Annual Report
2 (Moderate changes)	Site change within a contiguous campus or between facilities in adjacent city blocks using same equipment, SOPs, environment conditions (temperature and humidity), and controls, no changes made to manufacturing batch records	i. <i>Chemistry</i> : Updated batch records, compendial release, Stability: Long-term stability on one batch reported in Annual Report ii. <i>Dissolution</i> : Compendial release iii. <i>In Vivo BE</i> : None	Changes Being Effected (CBE) Supplement, Annual Report
3 (Major changes)	Changes in manufacturing site to a different campus. Same equipment, SOPs, environment conditions and controls should be used at the new site. No changes in the manufacturing batch records	i. <i>Chemistry</i> : Updated batch records, compendial release, Stability: 3 months' accelerated stability data reported in supplement, long-term stability data on up to three batches in Annual Report ii. <i>Dissolution</i> : Case B of the guidance, multipoint profile in compendial medium at 15, 30, 45, 60, and 120 min or until an asymptote is reached. Dissolution profile should be similar at both current and proposed site iii. <i>In Vivo BE</i> : None	Changes Being Effected (CBE) Supplement, Annual Report

III. Changes in Batch Size:

Post-approval changes in the site 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.

A. Level 1 Changes:

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 batches of the same design and operating principles;
- 2) The batch is manufactured in full compliance with CGMP's.

B. Level 2 Changes:

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 is of the same design and operating principles
- 2) The batch is manufactured in full compliance with CGMP's.

TABLE 3 Batch Size Change

Level	Definition	Test documentation	Filing documentation
1 (Minor changes)	Change in batch size by 10 times the pilot/bio-batch using equipment having the same design and operating principles as that used to produce the test batch. The batch should be manufactured under full compliance with cGMPs and SOPs using the same formulation and manufacturing procedures	<ol style="list-style-type: none">i. <i>Chemistry</i>: Compendial release, notification of changes, and updated batch records in annual report, <i>Stability</i>: Long-term stability on one batchii. <i>Dissolution</i>: Compendial releaseiii. <i>In vivo BE</i>: None	Annual Report including long-term stability data
2 (Moderate changes)	Change in batch size beyond a factor of 10 times the size of the pilot/ bio-batch using equipment having the same design and principles. The batch should be manufactured under full compliance with cGMPs and SOPs using the same formulation and manufacturing procedures	<ol style="list-style-type: none">i. <i>Chemistry</i>: Compendial release, notification of change, and updated batch records, <i>Stability</i>: 3 month accelerated stability and long-term stability on one batchii. <i>Dissolution</i>: Case B of the guidance, multiple point profile in compendial medium at 15, 30, 45, 60, and 120 min or until an asymptote is reachediii. <i>In vivo BE</i>: None	Changes Being Effected Supplement, Annual Report including long-term stability data

IV. Manufacturing:

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

A. Equipment 1:

1. Level 1 Changes:

This category consists of:

- 1) Change from non-automated or no mechanical equipment to automated or mechanical equipment to move ingredients
- 2) Change to alternative equipment of the same design and operating principles of the same or of a different capacity.

2. Level 2 Changes:

Change in equipment to a different design and different operating principles.

TABLE 4 Equipment Change

Level	Definition	Test documentation	Filing documentation
1	a. Changes from nonautomated to automated equipment to move ingredients b. Changes to alternative equipment of the same design and operating principles (same or different capacity)	i. <i>Chemistry</i> : Notification of change, compendial release, and Updated batch records Stability: Long-term stability on one batch ii. <i>Dissolution</i> : Compendial release iii. <i>In vivo BE</i> : None	Annual Report including long-term stability data
2	Changes in equipment to a different design and Different operating principles.	i. <i>Chemistry</i> : Compendial release, notification of change, updated batch records Stability: (a) Significant body of data available, which includes 3 months' accelerated stability data in supplement and long-term stability on one batch reported in Annual Report; (b) significant body of data not available, Which includes 3 months' accelerated stability on up to three batches in supplement and long-term stability on up to three batches reported in annual report ii. <i>Dissolution</i> : Case C dissolution profile of the guidance, which is multipoint dissolution, provides in water, 0.1N HCl, and USP buffer media at pH 4.5, 6.5, and 7.5 for the proposed and currently accepted formulation iii. <i>In vivo BE</i> : None	Prior Approval Supplement with justification for change, Annual Report including long-term stability data

B. Process 1:

1. Level 1 Changes:

This category includes process changes including changes such as admixing times and operating speeds within application/validation ranges.

2. Level 2 Changes:

This category includes process changes including changes such as admixing times and operating speeds outside of application/validation ranges.

3. Level 3 Changes:

This category includes changes 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.

TABLE 5 Process Change

Level	Definition	Test documentation	Filing documentation
1	Changes such as mixing times and operating speeds within application/validation changes	<ul style="list-style-type: none"> i. <i>Chemistry</i>: Compendial release ii. <i>Dissolution</i>: Compendial release. iii. <i>In vivo BE</i>: None 	Annual Report
2	Any changes outside of application/validation ranges (mixing time, operating speed)	<ul style="list-style-type: none"> i. <i>Chemistry</i>: Compendial release, notification of change, updated batch records Stability: Long-term stability on one batch ii. <i>Dissolution</i>: Case B dissolution profile of the guidance, multipoint dissolution in the application/compendial medium at 15, 30, 45, 60, and 120 min or until an asymptote is reached iii. <i>In vivo BE</i>: None 	Changes Being Effected (CBE) Supplement, Annual Report including long-term stability data
3	Any change in process such as wet-granulation to direct compression	<ul style="list-style-type: none"> i. <i>Chemistry</i>: Compendial release, notification of change, updated batch records Stability: (a) Significant body of data available, which is 3 months' accelerated stability on one batch in supplement and long-term stability on one batch reported in Annual Report; and (b) significant body of data not available 3 this includes 3 months' accelerated stability on up to three batches in supplement and long-term stability on up to three batches reported in Annual Report. ii. <i>Dissolution</i>: Case B dissolution profile of the guidance, multipoint dissolution profile in the application/compendial medium at 15, 30, 45, 60, and 120 min or until an asymptote is reached iii. <i>In Vivo BE</i>: Full BE study. BE study may be waived if <i>IVVC</i> is established 	Prior Approval Supplement with justification, Annual Report including long-term stability data

POST MARKETING SURVEILLANCE

○ INTRODUCTION:

- Post marketing surveillance is the practice of monitoring the safety of a pharmaceutical drug or medical device after it has been released on the market and is an important part of the science.
- To market a drug, the manufacture must provide evidence of its efficacy and safety to the **US Food and Drug Administration (FDA)**.
- It plat an important role to discover an undesirable effect that might present at risk.

- According to 21 CFR 314.80(a), an adverse drug experience is defined as “any adverse event associated with the use of a drug in humans, whether or not considered drug related”.
- The definition continues by stating that adverse events include those that occur in the course of the use of a drug product in professional practice, occur from drug overdose(accidental or intentional), abuse, or withdrawal, or involve failure of expected pharmacological action.
- It is important to examine who is involved in the process of ADE reporting.
- Generally, there are three members that take part in this process: a reporter, a manufacturer, and the FDA.
- The reporter can be a patient, doctor, pharmacist, nurse, or any one else aware of such an event.

- In 1960, two serious drugs reaction were observed in many patient. Eg. The drug **Thalidomide**, taken worldwide and causes limb deformities(phocomelia).
- In Japan, optic nerve damage was observed due to the adverse effect of drug clioquinol.
- Once the FDA approves a generic drug product, manufacturers are responsible for conducting post-marketing surveillance.
- Post-marketing reporting requirements for an approved ANDA are set forth in the US Federal Code of Regulations, 21CFR 314.80 (5) and 314.98.
- The main component of this requirement is the reporting of **adverse drug experiences(ADEs)**.

NEEDS OF PMS:

- The primary objective of PMS is to develop information about the drug effects under customary condition of drug use.
- Rare adverse events may not be detected in pre licensure studies because in very large clinical trials have limitation.
- Access to more patient and given data.

SOURCES OF PMS INFORMATION:

- Customer surveys.
- Literature reviews.
- Expert user groups.
- Customer complaints.
- The media etc.

METHODS OF SURVEILLANCE:

- Thus, four types of studies are generally used to identify drugs effect:
- Controlled clinical trials,
- Spontaneous or voluntary recording
- Cohort studies
- Case control studies

○ **CONTROLLED CLINICAL TRIALS:**

- To minimize bias through such method as randomization.
- Directly monitor patients for the duration of studies.
- For evaluating a drug's efficacy and safety.
- They are often costly.

○ **SPONTANEOUS REPORTING:**

- A communication from an individual (e.g.: health care professionals, consumer) to a company or regulatory authority.
- This describes a suspected adverse events.
- But the actual incidence of adverse drug reaction can not be determined through spontaneous reporting.

- **COHORT STUDIES:**

- Studies follow a defined group of patient for a period of time.
- Patient are not randomly assigned.

- **CASE CONTROL STUDIES:**

- Case control studies identify patient with the adverse effect to be studied, compare them with the sample drawn from the same cohort that rise to cases.

MANUFACTURER PMS SYSTEM:

- These are some of the type of knowledge and feed back which can achieved from a PMS system.
- Detection of some manufacturing problems.
- Product quality improvement.
- Conformation (or otherwise) of risk analysis.
- Knowledge of long term performance/reliability and / or chronic complication.
- Feedback on indication of use.
- Feedback on instruction for use.
- Feedback on use with other devices.
- Feedback on customer satisfaction.
- Feedback on continuing market viability.

SOP FOR POST-MARKETING SURVEILLANCE:

- Procedure related to drug use-results surveys.
- Procedures related to post-marketing clinical studies.
- Standards related to in-house inspections.
- Procedures related to the outsourcing of duties in post-marketing surveys, etc.
- Procedures related to the preservation of records involving duties in post-marketing surveys, etc.
- Any other procedures necessary for appropriate and smooth implementation of post-marketing surveys, etc.

THANK YOU!