Scale-Up and Post Approval Changes (SUPAC)

What is SUPAC?

- In the process of developing new drug product , the batch size used in earliest clinical and stability studies are small.
- The sizes of the batch is then increased (scale up).
- The scale up 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 (SUPAC)

What is SUPAC?

- The FDA has issued various guidance for SUPAC changes such as:
  - SUPAC-IR (immediate release solid oral dosage form .
  - SUPAC-MR (for modified release solid oral dosage form)
  - SUPAC-SS (for non sterile semisolid dosage form including creams, ointements, gels and lotions)
  - SUPAC: Manufacturing Equipment Addendum

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Rationale of SUPAC guidelines

- to speed up the processes of post approval changes of drug products
- FDA can assure their safety and effectiveness.
- lower the regulatory burden for industry.

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SUPAC guidelines

These guidelines provide recommendation for post approval changes in:

- component or composition
- the site of manufacture
- the scale up of manufacture
- the manufacturing process
- the manufacturing equipment

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SUPAC guidelines

The guidance defines:

- levels of change;
- recommended chemistry, manufacturing, and controls (cmc) tests for each level of change;
- *in vitro* dissolution tests and/or *in vivo* bioequivalence tests for each level of change; and
- documentation that should support the change.

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Levels of changes

- **Level 1 changes** are those that are **unlikely** to have any detectable impact on formulation quality and performance.
- **Level 2 changes** are those that **could** have a significant impact on formulation quality and performance.
- **Level 3 changes** are those that are **likely** to have a significant impact on formulation quality and performance.

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SUPAC-IR

Level 1 changes examples:

- 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
- Minor changes in excipients according to Table 1

Level	Excipients	% Change (w/w_{total}) Allowed
I	- Glidant: Talc; Other - Disintegrant: Starch; Other - Binder - Lubricant: Ca/Mg Strt; Other - Filler - Film Coat	+/- 1.0%; +/- 0.1% +/- 3.0%; 1.0% +/- 0.5% +/- 0.25%; +/-1.0% +/- 5.0% +/- 1.0%

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SUPAC-IR

LEVEL 1: 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.

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Example: SUPAC-IR

Level 2 changes examples:

- a. Change in the technical grade of an excipient. (Example: Avicel PH102 vs. Avicel PH200.)
- b. Changes in excipients, expressed as percent (w/w) of total formulation, greater than those listed for Level 1 change but less than or equal to the following percent ranges (which represent a two fold increase over Level 1 changes):

Level	Excipients	% Change (w/w_{total}) Allowed
II	- Glidant: Talc; Other - Disintegrant: Starch; Other - Binder - Lubricant: Ca/Mg Strt; Other - Filler - Film Coat	+/- 2.0%; +/- 0.2% +/- 6.0%; 2.0% +/- 1.0% +/- 0.5%; +/-2.0% +/- 10.0% +/- 2.0%

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SUPAC-IR

LEVEL 2: Test Documentation

a. **Chemistry Documentation**

- Application/compendial release requirements and batch records.
- Stability testing: 1 batch with 3 months accelerated stability data in supplement and 1 batch on long-term stability.

SUPAC-IR

LEVEL 2: Test Documentation

b. **Dissolution Documentation**

Case A: High Permeability, High Solubility Drugs

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

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 product formulations should be similar

SUPAC-IR

LEVEL 2: Test Documentation

b. **Dissolution Documentation**

Case C: High Permeability, Low Solubility Drugs

Multi-point dissolution profiles should be performed in water, 0.1 N HCl, and USP 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% 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 product formulations should be similar.

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- Dissolution profiles may be compared using the following equation that defines a similarity factor (f_2):

$$f_2 = 50 \text{ LOG } \{[1+1/n \sum_{t=1}^{n} (R_t-T_t)^2]^{-0.5} \text{ x } 100\}$$

- 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.

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SUPAC-IR LEVEL 2: Test Documentation

LEVEL 2: Test Documentation

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.

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Level 3 changes examples:

- Any qualitative and quantitative excipient changes to a narrow therapeutic drug beyond the ranges noted in Level 1
- All other drugs not meeting the dissolution criteria for Level 2
- Changes in the excipient ranges of low solubility, low permeability drugs beyond those listed for Level 1
- Changes in the excipient ranges of all drugs beyond those listed for Level 2.

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Level 3 : Test Documentation

- Application/compendial release requirements and batch records.

Significant *body of information 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 information not available:

- Up to three batches with three months accelerated stability data reported insupplement; one batch on long-term stability data reported in annual report.

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Level 3 : Test Documentation

Dissolution Documentation

Case B dissolution profile as described for level 2.

In Vivo Bioequivalence Documentation

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

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Table 1

Level	Excipients	% Change (w/w_{total}) Allowed
I	- Glidant: Talc; Other - Disintegrant: Starch; Other - Binder - Lubricant: Ca/Mg Strt; Other - Filler - Film Coat	+/- 1.0%; +/- 0.1% +/- 3.0%; 1.0% +/- 0.5% +/- 0.25%; +/-1.0% +/- 5.0% +/- 1.0%
II	- Glidant: Talc; Other - Disintegrant: Starch; Other - Binder - Lubricant: Ca/Mg Strt; Other - Filler - Film Coat	+/- 2.0%; +/- 0.2% +/- 6.0%; 2.0% +/- 1.0% +/- 0.5%; +/-2.0% +/- 10.0% +/- 2.0%
III	- Higher than SUPAC-IR Level 2 Excipient ranges	

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LEVEL 1

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 or Magnesium Stearate	±0.25
	Other	±1
Glidant	Talc	±1
	Other	±0.1
Film Coat		±1

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SUPAC-IR

Level 3 : Test Documentation

Filing Documentation

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

Component and composition changes

- Focus on the changes in amount of excipients in the drug product
- Not focus on change in the amount of the drug substance.