SUPAC

Scale - Up and Post Approval Changes

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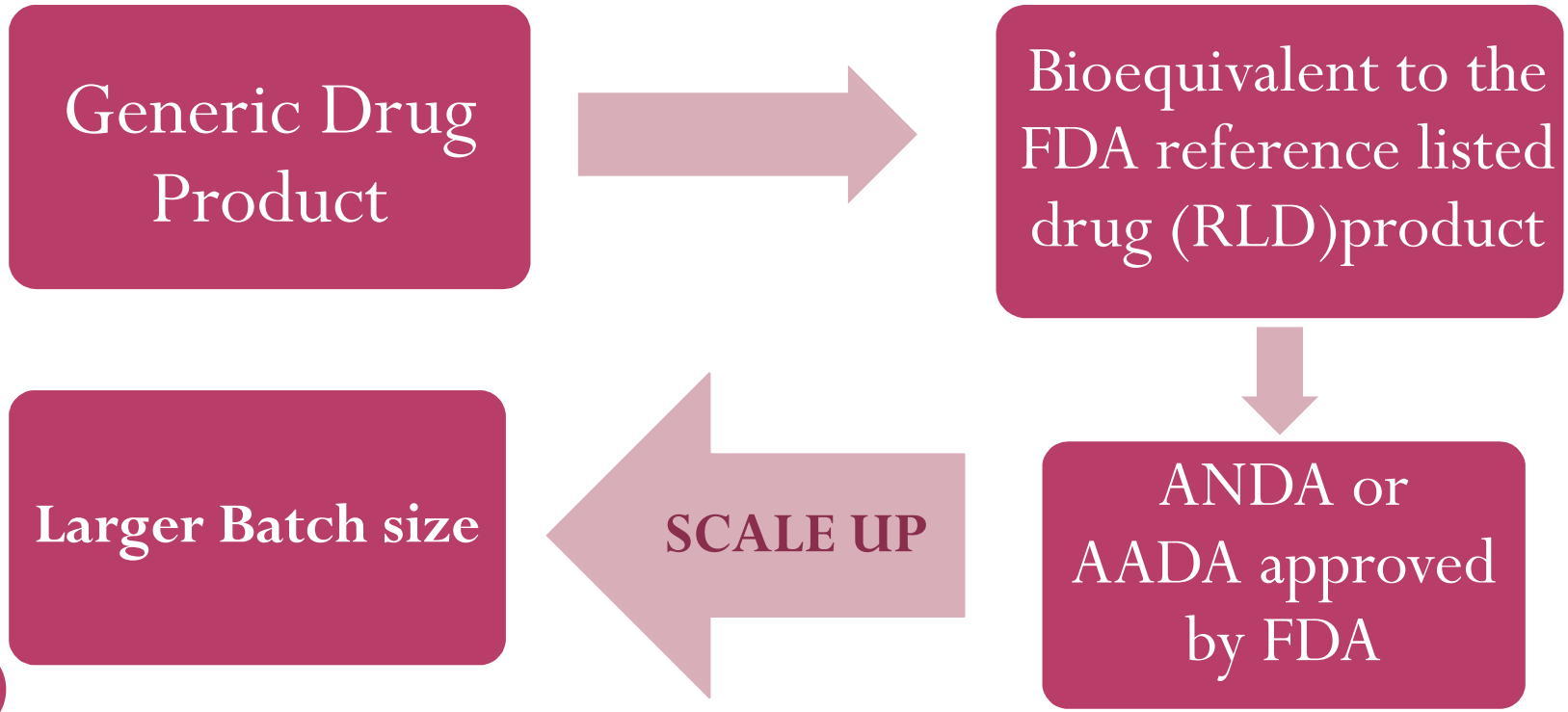
Generic Drug Product
Bioequivalent to the FDA reference listed drug (RLD)product
ANDA or AADA approved by FDA
SCALE UP
Larger Batch size

What is SUPAC

- In the process of developing a new drug product, the batch sizes used in the earliest human studies are small.

  The size of the batches is gradually increased (Scale - up).

- 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.**

Scientific Rationale

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

- The FDA has issued various guidance's for SUPAC changes designated as

A. SUPAC-IR (for immediate-release solid oral dosage forms),

B. SUPAC-MR (for modified-release solid oral dosage forms), and

C. SUPAC-SS (for non-sterile semisolid dosage forms including creams, ointments, gels, and lotions).

SUPAC GUIDELINES - DEFINE

Levels of change

Likelihood of impact on formulation quality and performance

- Level 1: **unlikely** to have detectable impact
- Level 2: **could have** significant impact
- Level 3: **likely** to have significant impact

Levels of change Cont . . .

Likelihood of impact on formulation quality and performance

- Level 1: Those changes that are unlikely to have any detectable impact on formulation quality and performance. **Example** Changes in the color, flavors and Changes in the excipient express as the percentage (w/w) of total formulation, less than or equal to the following range
- Level 2: Changes are those that could have significant impact on the formulation quality and performance. **Example** Changes in the technical grade of excipient (Avicel PH102 vs. Avicel PH200) Changes expressed as percent (w/w of total formulation) Level 2 Change
- Level 3: Level 3 changes are those that are likely to have significant impact on formulation quality and performance. **Example** Any qualitative or quantitative excipient changes to a narrow therapeutic drug beyond the range for level 1 All other drug not meeting the dissolution criteria as level 2.

- These guidelines provide recommendations for post approval changes in

(1) The components or composition,

(2) The site of manufacture,

(3) The scale-up of manufacture, and

(4) The manufacturing (process and equipment)

1) Components & Composition

- This section focuses on changes in excipients in the drug product
- SUPAC-MR: Excipient critical or non critical to the drug release.

  - Changes in non release controlling excipients

  - Changes in release controlling excipients
- SUPAC-SS: Changes in preservative

SUPAC - IR

LEVEL	CLASSIFICATION	EXCIPIENT RANGES (%w/w of total formulation)	TEST DOCUMENTATION	FILING DOCUMENTATION
I	-Deletion or partial deletion of an ingredient (colour, flavor or change in ingredient of the ink) -Changes in excipients, expressed as % (w/w) of total formulation, less than or equal to excipient % ranges	Filler ±5 Disintegrant Starch ±3 Other ±1 Binder ±0.5 Lubricant Calcium (Ca) or Magnesium (Mg) Stearate ±0.25 Other ±1 Glidant Talc ±1 Other ±0.1 Film Coat ±1	-stability -application/ compendial requirements	•Annual report

LEVEL	CLASSIFICATION	EXCIPIENT RANGES (%w/w of total formulation)	TEST DOCUMENTATION	FILING DOCUMENTATION
II	-change in technical grade of excipients -Changes in excipients, expressed as % (w/w) of total formulation, greater than Level 1 changes.	Filler ±10 Disintegrant Starch ±6 Other ±1 Binder ±1 Lubricant Calcium (Ca) or Magnesium (Mg) Stearate ±0.5 Other ±2 Glidant Talc ±2 Other ±0.2 Film Coat ±2	-stability application/compendial requirements -Dissolution data depends on solubility, theraputic range and permeability. Case A : High Permeability, High Solubility Drugs Single point Dissolution profile . Case B : Low Permeability, High Solubility Drugs Multi point dissolution profile Case C :High Permeability, Low Solubility Drugs Multi point and multi media dissolution profile	•Prior approval supplement •Annual report

LEVEL	CLASSIFICATION	TEST DOCUMENTATION	FILING DOCUMENTATION
III	-Higher than SUPAC-IR Level 1 and Level 2 excipient ranges.	-stability application/compendial requirements -Case B dissolution profile (Multi-point dissolution profile in the application /compendial medium at 15, 30, 45, 60, and 120 minutes or until an asymptote is reached for the proposed and currently accepted formulation.) -Biostudy or IVIVC	•Prior approval supplement •Annual report

SUPAC – MR Non Release Controlling Excipients

LEVEL	CLASSIFICATION	TEST DOCUMENTATION	FILING
I	-Delition or partial delition of an ingredient -upto SUPAC-IR Level 1 excipient ranges	-stability -application/compendial requirements	•Annual report
II	-change in technical grade of excipients -upto SUPAC-IR Level 2 excipient ranges	-stability application/compendial requirements -Multi-point dissolution profiles (15,30,45,60 & 120 min) USP buffer media at pH 4.5-7.5 for extended release) Three different Media (e.g., Water, 0.1N HCl, and USP buffer media at Ph 4.5 And 6.8 for delayed release)	•Prior approval supplement •Annual report
III	-Higher than SUPAC-IR Level 1 and Level 2 excipient ranges.	-stability application/compendial requirements -Biostudy or IVIVC	•Prior approval supplement •Annual report

SUPAC – MR Release Controlling Excipients

LEVEL	CLASSIFICATION	TEST DOCUMENTATION	FILING DOCUMEN-TATION
I	-≤ 5% w/w change based on total release controlling excipient content. -No other changes	-stability -application/compendial requirements	•Annual report
II	-change in technical grade of excipients -≤ 10% w/w change based on total release controlling excipient content.	-stability application/compendial requirements -Multi-point dissolution profiles (15,30,45,60 & 120 min) USP buffer pH 4.5-7.5 for extended release) Three different Media (e.g., Water, 0.1N HCl, and USP buffer media at Ph 4.5 And 6.8 for DR release)	•Prior approval supplement •Annual report
III	-> 10% w/w change based on total release controlling excipient content.	-stability application/compendial requirements -Biostudy or IVIVC	•Prior approval supplement •Annual report

SUPAC – SS Components and Composition

LEVEL	CLASSIFICATION	TEST DOCUMENTATION	FILING
I	-Delition or partial delition of an ingredient -change in supplier or technical grade of any other excipient -Upto 5 % change in approved amount of ingredient.	-stability -application/ compendial requirements	•Annual report
II	-Upto >5 % and ≤ 10 % change in approved amount of ingredient. -Change in particle size distribution of the drug substance, if the drug is in Suspension -change in supplier or technical grade of any other excipient	-stability application/compendial requirements -in vitro release test	•Changes being effected supplement •Annual report
III	-change in approved amount of ingredient. -Change in crystalline form of the drug substance, if the drug is in suspension	-stability application/compendial requirements -in vitro release test -in vivo bioequivalence test.	•Prior approval supplement •Annual report

SUPAC – SS Components and Composition - Preservative

LEVEL	CLASSIFICATION	TEST DOCUMENTATION	FILING
I	Quantitatively 10% or less change in the approved amount of preservative	-application/compendial requirements -Preservative effectiveness test at lowest specified preservative level	•Annual report
II	10% -20 % change in the approved amount of preservative	-application/compendial requirements -Preservative effectiveness test at lowest specified preservative level	•Changes being effected supplement •Annual report
III	> 20% change in the approved amount of preservative (including deletion) or use of a different preservative.	-application/compendial requirements -executed batch records -For new preservative: analytical method for identification and assay; validation studies -Preservative effectiveness test at lowest specified preservative level	•Prior approval supplement •Annual report

2) Manufacturing Site Changes

- changes in location of the site of manufacture, packaging operations and/or analytical testing laboratory
- do not include any scale-up changes, changes in manufacturing (including process and/or equipment), or changes in components or composition.
- current Good Manufacturing Practice (CGMP) inspection.

LEVEL	CLASSIFICATION	TEST DOCUMENTATION	FILING DOCUMENTATI-ON
I	-Site change within a single facility -No change in SOP, environmental conditions or equipments used -Common personnels	application/compendial requirements	•Annual report

LEVEL	CLASSIFICATION	TEST DOCUMENTATION	FILING
II	-Same continuous campus -Common personnel -No other changes	-application/compendial requirements -Notification of Location of new site -Updated batch records SUPAC – MR -Multi-point dissolution profiles (15,30,45,60 & 120 min) USP buffer media at pH 4.5-7.5 for extended release) Three different Media (e.g., Water, 0.1N HCl, and USP buffer media at Ph 4.5 And 6.8 for delayed release)until 80% of Drug Released.	•Annual report •Changes being Effected Supplement

LEVEL	CLASSIFICATION	TEST DOCUMENTATION	FILING
III	-Different campus -Different personnel	-application/compendial requirements -Notification of Location of new site -Updated batch record SUPAC –IR Multi-point dissolution profile in the application/compendial medium SUPAC – MR -Multi-point dissolution profiles (15,30,45,60 & 120 min) USP buffer media at pH 4.5-7.5 for extended release) Three different Media (e.g., Water, 0.1N HCl, and USP buffer media at Ph 4.5 And 6.8 for delayed release) untill 80 % of drug released.	Annual report Prior approval supplement

3) Batch Size Change (Scale Up)

- changes in the size of a batch from the pivotal/pilot scale biobatch material to larger production batches
- compliance with CGMP's
- No change in SOP, formulation and manufacturing procedures or equipments used
- All scale-up changes should be properly validated
- the minimum batch size for the pivotal clinical trial batch or biobatch be at least **100000 dosage units /100 kg or 10%** of a production batch, whichever is larger.

LEVEL	CLASSIFICATION	TEST DOCUMENTATION	FILING
I	Change in batch size, up to and including a factor of 10 times the size of the pilot/biobatch	Updated batch records application/compendial requirements stability	•Annual report
II	Changes in batch size beyond a factor of ten times the size of the pilot or biobatch, No other changes	-Updated batch records -application/compendial requirements -Stability SUPAC –IR Multi-point dissolution profiles SUPAC – MR -Multi-point dissolution profiles in multiple medias (e.g., USP buffer media at pH 4.5-7.5 for extended release) three other media (e.g., Water, 0.1N HCl, and USP buffer media at Ph 4.5 And 6.8 for delayed release) SUPAC-SS In vitro release test Documentation	•Annual report •Changes being Effected Supplement

4) Manufacturing Changes

- Changes affecting:
  - Equipments
  - Manufacturing process

- Appropriate validation studies are conducted

Manufacturing Changes - Equipments

LEVEL	CLASSIFICATION	TEST DOCUMENTATION	FILING
I	-Alternate equipment of same design and principles Automated equipments	-Updated batch records -application/compendial requirements stability	•Annual report
II	Change to equipment of different design and principle	Updated batch records application/compendial requirements Stability SUPAC –IR Multi-point dissolution profiles in multiple medias SUPAC – MR -Multi-point dissolution profiles in multiple medias SUPAC-SS In vitro release test Documentation	•Annual report •Changes being Effected Supplement

Manufacturing Changes- Process

LEVEL	CLASSIFICATION	TEST DOCUMENTATION	FILING
I	-Adjustment of equipment operating conditions (operating speeds, mixing times) <u>Within approved application ranges</u>	-Updated batch records -application/compendial requirements -stability	•Annual report

LEVEL	CLASSIFICATION	TEST DOCUMENTATION	FILING
II	-Adjustment of equipment operating conditions (operating speeds, mixing times) <u>Beyond approved application ranges</u> -SUPAC – SS Change in the process of combining two phases	-Updated batch records -application/compendial requirements -Stability SUPAC-IR Multi-point dissolution profile SUPAC-MR -Multi-point dissolution profiles in multiple medias (e.g., USP buffer media at pH 4.5-7.5 for extended release) three other media (e.g., Water, 0.1N HCl, and USP buffer media at Ph 4.5 And 6.8 for delayed release) SUPAC-SS In vitro release test Documentation	•Annual report •Changes being Effected Supplement

LEVEL	CLASSIFICATION	TEST DOCUMENTATION	FILING
III (SUPAC-IR SUPAC-MR)	Changes in the type of process used (e.g. wet granulation to direct compression	-Updated batch records -application/compendial requirements -Stability -Biostudy or IVIVC SUPAC-IR Multi-point dissolution profile SUPAC-MR Multi-point dissolution profiles in multiple medias (e.g., USP buffer media at pH 4.5-7.5 for extended release) three other media (e.g., Water, 0.1N HCl, and USP buffer media at Ph 4.5 And 6.8 for delayed release)	•Prior approval supplement •Annual report

Dissolution Profile Comparison Using Similarity Factor, f2

- FDA has placed more emphasis on a dissolution profile comparison in the area of post-approval changes
- Among several methods investigated for dissolution profile comparison, f2 is the simplest.
- $f_2 = 50 + \log \{[1+ (1/n) \sum_{t=1} * n (R_t-T_t)^2]^{-0.5} *100\}$ (where Rt and Tt are the cumulative percentage dissolved at each of the selected n time points of the reference and test product respectively.
- When the two profiles are identical, f2=100. FDA has set a public standard of f2 value between 50-100 to indicate similarity between two dissolution profiles.

SUPAC limitations

- SUPAC:
  - ▶ has not been updated (1995/97 for main guides)
  - ▶ does not discuss multiple **changes**
  - ▶ does not cover modified equipment
  - ▶ must be used in conjunction with other references, e.g. excipient handbook

Thank You