SUPAC OF IMMEDIATE-RELEASE, MODIFIED- RELEASE AND SEMI-SOLID: 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 IR, MR, SS, 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.
- 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.
- For example, a change in the inactive ingredient beyond a certain range will have more effect on a modified- release (MR) dosage form than it would on an immediate - release (IR) dosage form, where bioavailability is not rate limiting.
- Likewise, a change in the primary packaging of liquid Parenteral may have more pronounced effect on its effectiveness than it would have on a solid dosage form.

Scientific & Regulatory Rational for SUPAC

Authorities Regulations like FDA (U.S. Food and Drug Administration), the European Commission, the Agencia Nacional de Vigilancia Sanitaria (ANVISA) (in English the National Health Surveillance Agency — Brazil, and others require the pharmaceutical industries in respective

countries to follow guidelines on scale- up and post approval changes (SUPAC) to maintain the quality of the pharmaceutical produced.

The SUPAC guidance published by the FDA define various levels of change and for each level of change specifies the:

1) Recommended chemistry, manufacturing, and control tests;
2) In-vitro dissolution testing and/or in-vivo bioequivalence tests; and
3) Documentation that the FDA requires to be filed in the NDA, ANDA, or AADA to support the change.(1)

SUPAC-IR – Implementation

- Federal Register notice - November 30, 1995
- Industry training - February 15, 1996
- Updated via letter - February 18, 1997
- Working Group revising the guidance
- Applies to immediate release tablets, chewable tablets, capsules, and soft gelatin.

SUPAC-MR - IMPLEMENTATION

- Federal register notice - October 6, 1997
- Industry training - November 24, 1997
- Applies to modified release, solid, oral dosage forms

SUPAC-SS – Implementation

- Federal register notice - June 13, 1997
- Industry training - May 29, 1997
- Applies to non-sterile semi-solid preparations, e.g., creams, gels, and ointments. (2)

METHOD AND ILLUSTRATIONS

Components & Compositions Changes: Components & composition changes includes mainly three levels of changes like I, II, III.

Level I Changes: Level 1 changes are minor changes those that are unlikely to have any makeable effect on quality of formulae and the action.

Examples
- deletion of color or flavor
- Excipients change with total additive effect of up to 5%

Table 1: Allowable percentages changes in Excipients in SUPAC (3)

Excipients	Percentage Excipients (w/w) out of total target dosage form weight
Filler	± 5
Disintegrate	-
Starch	± 3
Other	± 1
Binder	± 0.5
Lubricant	-
Calcium or magnesium Stearate	± 0.25
Other	± 1
Glidant	-
Talc	± 1
Other	± 1
Film coat	± 1

Table 2: Test Documentation for Level I Changes (4)

Test Documentation	IR (Immediate release)	SS (Semisolid)	MR	
			Non-release controlling Excipients	Release controlling Excipients
Chemistry documentation	Application or compendia release requirement			
Stability testing	One batch with long term stability testing (1 LT)	1st batch with Long Term stability study		
Dissolution Documentation	None			
In vivo				
Filling documentation	Annual report (all information including LT)			

Level-II Changes: Those that are moderate changes could have significant impact on formulation quality & performance. Tests & filling documentations for level-II changes vary depending on three factors: therapeutic range, solubility, permeability, e.g. Change in technical grade of Excipients, Excipients change with total additive effect of up to 10%.Changes in % of Excipients are as like table 1 & test documentation for level 2 changes are as follows:

Table 3: Test Documentation for Level-2 Changes (5)

Test Documentation	IR (Immediate release)	SS (Semisolid)	MR	
			Non-release controlling Excipients	Release controlling Excipients
Chemistry documentation	Release & batch record	Release & executed batch record		
Stability testing	One batch with 3 months accelerated stability study and one batch with long term stability study			
Dissolution Documentation	Yes depends on permeability & solubility & compare as per dissolution documentations			
In vivo	None		Non for non-narrow therapeutic index (T.I.)AND single dose for narrow T.I.	
Filling documentation	PA(Prior Approval all data including accelerated stability data) AR(Annual report long term stability data)			

Dissolution documentation is as per below in Table: 4

Table 4: Dissolution documentation of Level-II Changes (6)

Cases	Parameters	Documentation
A	High Solubility & high permeability	85% Dissolution in 900 ml and 15min of 0.1 N HCl. If a drug product fails to meet this criterion, the applicant should perform the tests described for Case B or C as below.
B	Low	Multipoint dissolution profile should be performed in the

	permeability & high solubility	application/compendia 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 formulation should be similar.
C	High permeability & low solubility	Multipoint 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 suspected and routine 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 routine used formulae should be similar.

Level III Changes: Those that are major changes could have significant impact on formulation quality & performance

Tests and filing documentation very depending on the following three factors:

- therapeutic range
- solubility
- permeability

Examples:

- Any quality & quantity changes in narrow prescription drugs.
- The different formulations not meeting dissolution criteria.
- Changes in Excipients range of low solubility, low permeability drugs
- Changes in Excipients range of all other drugs.
- Changes in crystalline form of drug substance if drug formulations in suspensions.
- Changes in release controlling Excipients>10%
- Addition or deletion of release controlling Excipients(s). (7)

Table 5: Test Documentation for Level 3 Changes (8)

Test Documentation	IR (Immediate release)	SS (Semisolid)	MR	
			Non-release controlling Excipients	Release controlling Excipients
Chemistry documentation	Release & Batch records	Release & executed batch records		
Stability testing	One batch with 3 months accelerated stability study and one batch with long term stability study	Same and first three batches with LT		
Dissolution Documentation	Yes depends on permeability & solubility & compare as per dissolution documentations	Not required	Extended and delayed	
In vivo	Bioequivalence needed			
Filling documentation	PA(Prior Approval all data including accelerated stability data),AR(Annual report long term stability data)			

Extended Release: In addition to application /compendia release requirements, multipoint dissolution profiles should be obtained in three other media, for example, in water, 0.1 N HCl and USP buffer media at pH 4.5 and 6.8 for the changed drug product and the bio-batch or

marketed batch (unchanged drug product). Adequate sampling should be performed, for example, at 1, 2 and 4 hours and every two hours thereafter until either 80 % of the drug from the drug product is released or and asymptote is reached. A surfactant may be used with appropriate justification.

Delayed Release: In addition to application /compendia release requirements dissolution tests should be performed in 0.1 N HCl for 2 hours (acid stage) followed by testing in USP buffer media, in the range of pH 4.5-7.5 (buffer stage) under standard test conditions and two additional agitation speeds using the application/compendia test apparatus (three additional test conditions. If the application/compendia test apparatus is the rotating basked method (apparatus 1), a 50, 100 and 150 RPM rotation speed may be used. Multipoint dissolution profiles should be obtained in between buffer stage of process. Adequate sampling should be performed, for example, at 15, 30, 45, 60, and 120 minutes (following the time from which the dosage form is placed in the buffer) until either 80 % if the drug from the drug produce is release or an asymptote is reached. The above dissolution testing should be performed using the changed drug product and the bio-batch or marketed batch (unchanged drug product). (9)

Preservatives Changes: It is done with SUPAC-SS only, when quality & quantity changes are made & additional testing should be performed.

Table 6: Test Documentation of Preservatives in SUPAC-SS (10)

Test Documentation	Level-I	Level-II	Level-III
SUPAC-SS Quantity of approved preservatives	≤10% change	>10%≤20% change	>20% change (including deletion) or use of a different preservative
Chemistry	Application/compendia release requirements Preservative Effectiveness Test		Release requirements, Preservative Effectiveness Test, Analytical method for ID, Validation studies, Executed batch records
Filling	AR	CBE(Change Being Effected)	PA(Prior Approval all data including accelerated stability data),AR(Annual report long term stability data)
Stability testing	-	-	One batch with 3 months accelerated stability study and one batch with long term stability study.

Manufacturing Site Changes: Manufacturing site changes means changes in location sites only, no scale-up, no manufacturing changes, cGMPs.

Manufacturing Site Level I Changes: Level I changes is defined as changes in manufacturing site "within a single facility where the same equipment, SOPs, environmental conditions and controls, and personnel common to both sites are used."

Table 7: Test Documentations of Manufacturing site Level-I Changes

Test documentations	IR	SS	MR
Chemistry documentations	Release		

Dissolution	Release	None	Release
In vivo	None		
File	Annual Report		

Manufacturing Site Level II Changes: Level 2 changes may be defined as the changes in the manufacturing site "within a contiguous campus, or between facilities in adjacent city blocks, where same equipment, SOPs, environmental conditions and controls, and personnel common to both sites are used"

Table 8: Test Documentations of Manufacturing site Level-II Changes

Test documentations	IR	SS	MR
Chemistry documentation	Release; Notification of location of new site and updated batch record		Release; Notification of location of new site and updated executed batch record
Stability testing	One long term	First one term	One batch of three months accelerated study & first batch of long term stability study
Dissolution	Release	None	Extended & Delayed
In vivo	None		
File	Change Being Expected (Accelerated study) & Annual Report (Long term stability study)		

Manufacturing Site Level-III Changes: A change in manufacturing site to a different campus where same equipment, same environmental conditions and the same controls are used.

Table 9: Test Documentation of Manufacturing site Level-III Changes

Test documentations	IR	SS	MR
Chemistry documentation	Release notification of change & updated batch record		
Significant body of information available	One batch of three months accelerated study up to three batches with long term stability study.		
Significant body of information is not available	Up to three batches with three months accelerated study, first three production batches with long term stability study.		
Dissolution	As per low permeability & high solubility	Comparison	Extended & delayed
In-vivo	None		Single dose bioequivalence
File	Change being Expected(Accelerated study) & Annual Report(Long term stability study)		PA (Prior Approval all data including accelerated stability data) ,AR (Annual report long term stability data)

Batch Size Changes: Batch size changes include change to larger or small production

batch, less than 100000 units scale down not covered, Scale-up validation needed, may need inspection.

Batch Size Level-I Change: A change up to and including a factor of 10 times pilot/bio-batch where cGMPs, SOPs, controls, formulation, manufacturing procedures etc. are same.

Table 10: Test Documentation of Level-I Batch size Changes

Test documentations	IR	SS	MR
Chemistry documentation	Release notification of changes & updated batch records		
Stability study	One long term stability study		
In vivo	None		
Dissolution	Release	None	Release
File	Annual report (long term stability study)		

Batch Size Level-II Change: Defined as a change in batch size beyond a factor of 10 times the pilot / bio batch where cGMPs, equipment, SOPs and controls, formulation and manufacturing procedures are same.

Table 11: Test Documentation of Level-II Batch size Changes

Test documentation	IR	SS	MR
Chemistry documentation	Release notification of change & updated batch records		
Stability testing	One to three months accelerated study with one long term stability study		
Significant body of documentation	One batch with three months accelerated stability study & one long term stability study		Same three batch with long term stability study
Dissolution	As per low permeability high solubility	Comparison	Extended & delayed
In vivo	None		
File	Change being Expected (Accelerated study) & Annual Report (Long term stability study)		

Manufacturing Changes: It includes changes that may affect equipment's& changes that may affect the manufacturing process.

Equipment's Changes:

Equipments Changes to Level-I of Manufacturing changes: A change to automated or mechanical equip. to move ingredients, a change to alternative equipment of same design and operating principle, a change to different capacity equipment.(ISPE Equip addendum)

Table 12: Test Documentation of Level-I Changes of Equipment changes of Manufacturing changes

Test documentation	IR	SS	MR
Chemistry	Release notification of change & updated batch record		
Stability testing	One long term		
Dissolution	Released	None	Release
In vivo	None		
File	Annual report long term stability		

Equipments Changes to Level-II of Manufacturing changes: Changes in equipment to a different design or different operating principle or a change in the type of mixing equipment.

Table 13: Test Documentations of Level-II Changes Of Equipments changes of Manufacturing changes

Test documentation	IR	SS	MR
Chemistry documentations	Release notifications of changes & updated batch records		
Significant body of documentation	One batch with three months accelerated stability study & one long term stability study		Same three batch with long term stability study
Dissolution	As per high permeability & low solubility	Comparison	Extended & Delayed
In-vivo	None		
File	PA(Prior Approval all data including accelerated stability data),AR(Annual report long term stability data)	CBE(Change Being Effected) including accelerated stability data, AR(Annual report long term stability data)	PA(Prior Approval all data including accelerated stability data), AR(Annual report long term stability data)

Manufacturing Process Changes: Manufacturing Process Level-I Change: This category includes changes such as time of mixing and speeds of operating within application and validation ranges.

Table 14: Test Documentation of Manufacturing process Level-I changes

Test documentation	IR	SS	MR
Chemistry documentation	Release	Release	Release notification of change & updated executed batch record
Dissolution	Release	None	Release
In vivo	None		
File	Annual report		

Manufacturing Process Level-II Changes: This category includes changes such as time of mixing and speeds of operating outside of application and validation ranges

Table 15: Test Documentation of Manufacturing process Level-II changes

Test documentation		IR	SS	MR
Chemistry documentation		Release notification of change & updated batch records		
Stability testing		One long term	-	One batch with three months accelerated study &one long term stability study.
stability	Specific body of documentations	-	One batch with 3 months accelerated stability study.	-

			First long term stability study	
	Non-specific body of documentations	-	first three production batch with 3 months accelerated stability study	-
Dissolution		Low permeability high solubility	Comparison	Extended & delayed
File		CBE(Change Being Effected) including accelerated stability data, AR(Annual report long term stability data		

Manufacturing Process Level-III Changes: 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.

Table 16: Test Documentations of Manufacturing process Level-III changes

Test documentations		IR	SS	MR
Chemistry documentations		Release notifications of changes & updated batch records	No level-III changes	Release notifications of changes & updated executed batch records
Stability testing				Three batches with 3 months accelerated stability study, first three batches with long term stability study.
Stability	Specific body of documentations (SDB)	One batch with three months accelerated study & one long term stability study		
	Non-specific body of documentations (NSDB)	Up to 3 batch with 3 months accelerated stability study and up to 3 batch with long term stability study		
Dissolution		Low permeability high solubility		Extended & delayed
In vivo		Study needed		Single dose
File		PA(Prior Approval all data including accelerated stability data), AR(Annual report long term stability data)		PA(Prior Approval all data including accelerated stability data), AR(Annual report long term stability data)

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

- Reduced administrative costs for documentation of changes by the regulatory affairs departments
- Estimated saving $51.2 million/year.

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CONFLICT OF INTEREST

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