

M E M O R A N D U M

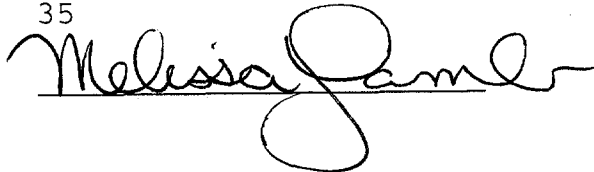
DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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Date: March 6, 2001  
To: Dockets Management Branch (HFA-305)  
From: Melissa Lamb  
Office of Generic Drugs  
Subject: Comparison of Supac-IR, MR & SS

This memorandum forwards overheads of a presentation to the Dockets Management Branch for inclusion in Docket 90S-0308. The following is information on the presentation for the Docket records:

Title of Presentation: Comparison of Supac-IR, MR & SS  
Presented for: Industry Exchange Meeting  
Date Presented: April 10, 2000  
Presented by: Vilayat S. Sayeed, Ph.D.  
Number of Pages: 35



Attachment

90S-0308

M699

**FDA/ISPE Scale-Up Post Approval Changes  
Industry Exchange Meetings  
Chicago, Illinois  
April 10, 2000**

**COMPARISON OF SUPAC-IR, MR & SS**

**Vilayat A. Sayeed, Ph.D.**

**Office of Pharmaceutical Science  
Center for Drug Evaluation & Research  
Food and Drug Administration**



## Guidances Define:

- levels of change
- CMC tests
- in vitro release tests and in vivo bio tests
- support documentation



## Components and Composition

- Focuses on changes in drug product excipients
- qualitative and quantitative changes are described
- chronology of changes needed



## Level I

### Examples

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

Δ ∴ ^

IR

SS

MR (nrc)

MR (rc)

Chem:	release	release	release	release
Stab-:	1 LT	1st LT	1st LT	1st LT
Dissol:	none	none	none	none
In Vivo:	none	none	none	none
File:	AR (LT stab)	AR (LT stab)	AR (LT stab)	AR (LT stab)

## Level 2

### Other Considerations

- therapeutic range
- solubility
- permeability

### Examples:

- change in technical grade of excipient
- excipient change with total additive effect of up to 10%



	<u>IR</u>	<u>SS</u>	<u>MR (nrc)</u>	<u>MR (rc)</u>
Chem:	release	release	release	release
Stab:	bat rec	exec bat rec	exec bat rec	exec bat rec
	1-3 mos acc	(same)	(same)	(same)
	1 LT	(same)	(same)	(same)
Dissol:	yes-depends on P&S	yes-compare	yes-compare	yes-compare
In Vivo:	none	none	none	none nonnarrow single dose narrow
File:	PA (accel stab) AR (LT stab)	CBE (accel stab) AR (LT stab)	PA (accel stab) AR (LT stab)	PA (accel stab) AR (LT stab)





## Level 3

### Other Considerations

- therapeutic range
- solubility
- permeability

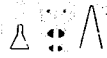


## Level 3

### Examples

- any Q&Q excipient change to narrow Rx drug
- other drugs not under other dissolution criteria
- changes in excipient range of lo-sol, lo perm
- changes in excipient range of all other drugs
- change in crystalline form
- change in release excipient > 10%
- addition or deletion of release excipient

	<u>IR</u>	<u>SS</u>	<u>MR (nrc)</u>	<u>MR (rc)</u>
Chem:	release bat rec	release exec bat rec	release exec bat rec	release exec bat rec
Stab SBD:	1-3 mos accel 1 LT	1-3 mos accel 1st 3 LT	1-3 mos accel 1st 3 LT	1-3 mos accel 1st 3 LT
Stab NSBD:	upto 3-3 mos acc 1 LT	3-3 mos accel 1st LT	3-3 mos accel 1st 3 LT	3-3 mos accel 1st 3 LT
Dissol:	same as level 2	not req.	extended & delayed	extended & delayed
In Vivo:	bio needed	bio needed	bio needed	bio needed
File:	PA (accel stab) AR (LT stab)	PA (accel stab) AR (LT stab)	PA (accel stab) AR (LT stab)	PA (accel stab) AR (LT stab)



## Preservative

- In SUPAC-SS only
- When any Q & Q change made
- Additional testing needed

## LEVEL 1 CHANGE

“ $\leq$  10% or less change in the amount of the approved preservative”

Chem: Appl. / compendial release requirements  
Preservative Effectiveness Test

File: AR

## LEVEL 2 CHANGE

“quantitatively  $> 10\% \leq 20\%$  change in the approved amount of preservative”

Chem: Appl. / compendial release requirements

Preservative Effectiveness Test

File: CBE

## LEVEL 3 CHANGE

Quantitatively > than 20% change in the approved amount of preservative (including deletion) or use of different preservative.

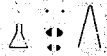
Chem: Release requirements  
Preservative Effectiveness Test  
Analytical method for ID  
Validation studies  
Executed batch records

Stab: 1-3 months accelerated  
1st production long term

File: PA (accel stab)  
AR (LT stab)

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## MANUFACTURING SITE CHANGE

- \* changes in site location only
- \* no scale-up
- \* no manufacturing changes
- \* CGMPs



## LEVEL 1 CHANGE

“within a single facility where the same equipment, SOPs, environmental conditions and controls, and personnel common to both sites are used”



IR

SS

MR

Chem:

release

release

release

Dissol:

release

none

release

In Vivo:

none

none

none

File:

AR

AR

AR

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## LEVEL 2 CHANGE

“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”

△ : ^

IR

SS

MR

Chem:

release

release

release

upd bat rec

upd bat rec

upd bat rec

location

location

location

Stab:

1 LT

1st LT

1-3 mos accel

1st LT

Dissol:

release

none

extended and delayed

In Vivo:

none

none

none

File:

CBE

CBE

CBE (accel stab)

AR (LT stab)

AR (LT stab)

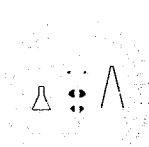
AR (LT stab)

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## LEVEL 3 CHANGE

A change in manufacturing site to a different campus where the same equipment, SOPs, environmental conditions and controls are used.



IR

SS

MR

Chem:	release upd bat rec location	release upd bat rec location	release upd bat rec location
Stab SBD:	1-3 mos acc 1 LT	1-3 mos acc 1st 3 LT	1-3 mos acc 1st 3 LT
Stab NSBD:	up to 3-3 mos acc up to 3 LT	3-3 mos acc 3 LT	3-3 mos acc 1st 3 LT
Dissol:	on lo-perm, hi sol	comparison	extended and delayed
In Vivo:	none	none	single dose bio
File:	CBE (accel stab) AR (LT stab)	CBE (accel stab) AR (LT stab)	PA (accel stab) AR (LT stab)

## BATCH SIZE

- \*change to larger or smaller production batch
- \*< 100,000 unit scale down not covered
- \*scale up validation needed
- \*may need inspection

## LEVEL 1 CHANGE

A change up to and including a factor of 10 times the pilot / bio batch where CGMPs, SOPs and controls, formulation and manufacturing procedures are same.



IR

SS

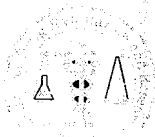
MR

Chem:	release notification upd bat rec	release notification upd bat rec	release notification exec bat rec
Stab:	1 LT	1st LT	1st LT
Dissol:	release	none	release
In Vivo:	none	none	none
File:	AR (LT stab)	AR (LT stab)	AR (LT stab)



## LEVEL 2 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.



IR

SS

MR

Chem:	release notification upd bat rec	release notification upd bat rec	release notification upd bat rec
Stab:	1-3 mos accel 1 LT	1-3 mos accel 1st LT	1-3 mos accel 1st LT
Dissol:	lo perm, hi sol	comparison	extended and delayed
In Vivo:	none	none	none
File:	CBE (accel stab) AR (LT stab)	CBE (accel stab) AR (LT stab)	CBE (accel stab) AR (LT stab)



## MANUFACTURING CHANGES

- \* change may affect equipment
- \* change may affect process

## EQUIPMENT LEVEL 1 CHANGE

A change to automated or mechanical to move ingredients, a change to alternative equipment of same design and operating principle (ISPE Equip addendum)

△ ∴ Λ

IR

SS

MR

Chem:	release notification upd bat rec	release notification upd bat rec	release notification upd bat rec
Stab:	1 LT	1 LT	1 LT
Dissol:	release	none	release
In Vivo:	none	none	none
File:	AR (LT stab)	AR (LT stab)	AR (LT stab)

## LEVEL 2 CHANGE



Defined as changes in equipment to a different design or different operating principle.  
(ISPE Equip addendum)



IR

SS

MR

Chem:	release notification upd bat rec	release notification upd bat rec	release notification upd exec bat rec
Stab SBD:	1-3 mos accel 1 LT	1-3 mos accel 1st LT	1-3 mos accel 3 LT
Dissol:	yes (Case C)	comparison	extended and delayed
In Vivo:	none	none	none
File:	PA (accel stab) AR (LT stab)	CBE (accel stab) AR (LT stab)	PA (accel stab) AR (LT stab)

# PROCESS

## LEVEL 1 CHANGE

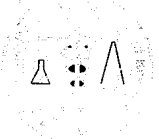
Defined as including mixing times and operating speeds within application / validation ranges.

IR

SS

MR

Chem:	release	release	release notification upd exec bat rec
Dissol:	release	none	release
In Vivo:	none	none	none
File:	AR	AR	AR



## LEVEL 2 CHANGE

Including mixing times and operating speeds outside of application / validation ranges.

Chem:	<u>IR</u> release notification upd bat rec	<u>SS</u> release notification upd bat	<u>MR</u> release notification upd bat rec
Stab:	1 LT		1-3 mos accel 1st LT
Stab SBD:		1-3 mos accel 1st LT	





IR

SS

MR

Stab NSBD:

3-3 mos accel

Dissol:

yes (Case B)

comparison

extended and delayed

In Vivo:

none

none

none

File:

CBE (accel stab)

CBE (accel stab)

CBE (accel stab)

AR (LT stab)

AR (LT stab)

AR (LT stab)

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### LEVEL 3 CHANGE

Including a change in the type of manufacturing process, such as wet granulation to compression of dry powder.

IR

SS

MR

Chem:

release

(No level 3)

release

notification

notification

uppd bat rec

uppd exec bat rec

Stab:

3-3 mos accel

Stab SBD:

1-3 mos accel

1 LT

1st 3 LT

Δ ∩ Λ

IR

SS

MR

Stab NSBD: up to 3-3 mos accel  
up to 3 LT

Dissol: yes (Case B)

extended and delayed

In Vivo: study needed

single dose

File: PA (accel stab)  
AR (LT stab)

PA (accel stab)  
AR (LT stab)

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