PHARMA DEVILS

QUALITY ASSURANCE DEPARTMENT

STANDARD OPERATING PROCEDURE	
Department: Formulation, Research and Development	**SOP No.:**
Title: To Define the Holding Times of the Intermediates	**Effective Date:**
Supersedes: Nil	**Review Date:**
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1.0 OBJECTIVE:

To lay down the procedure for defining holding times of the intermediates.

2.0 SCOPE:

This SOP is applicable to Formulations Research and Development.

3.0 RESPONSIBILITY:

3.1 FR&D personnel shall prepare the hold time study protocol and provide the samples to AD for analysis during development stage.

3.2 Group Leader – FR&D Shall review the protocol.

3.3 Head – FR&D for implementation and compliance of this procedure.

4.0 DEFINITION(s):

Not Applicable

5.0 PROCEDURE:

5.1 FR&D shall propose the tentative hold time of different intermediate stages for different formulation as per Annexure 01

5.2 The proposed hold time may vary based on the criticality of the molecule and type of formulation.

5.3 FR&D shall prepare hold time protocol as per the format as detailed in Annexure 01.

5.4 During the development, critical stages shall be identified to generate hold time data and the same shall be mentioned in the protocol for the study.

5.5 After approval of the protocol, hold time study shall be carried out.

5.6 Required quantity of sample as defined in Annexure 02 shall be collected at various stages of the process by FR&D personnel. The quantity may vary depending upon the criticality of the molecule and type of formulation.

5.7 The samples shall be collected in double line polybag/HDPE containers and shall be stored at 25°C±5°C/60%±5% RH.

5.8 Other suitable storage container and storage condition may be used based on the criticality of molecule and formulation.

5.9 The samples shall be analyzed by AD at different time intervals during the proposed hold time.

5.10 On completion of analysis of hold time study, the analytical data shall be compiled in the respective formats as detailed in Annexure 08.

5.11 Group Leader-FR&D shall review the compiled report.

5.12 Based on the review, the hold time shall be recommended at each of intermediate and shall be listed in the format as detailed in Annexure 09.

5.13 A copy of the recommended hold time shall be issued to respective manufacturing location for reference.

5.14 Any deviation from the recommended hold time shall be handled as per SOP on "handling of deviation".

5.15 Any change in recommended hold time shall be made as per SOP on "change control system".

6.0 REFERENCE(s):

SOP No. (Current version)	Title
	Change control system
	Handling of deviation

7.0 ABBREVIATION(s):

Abbreviation	Full Description
SOP	Standard Operating Procedure
QA	Quality Assurance
FR&D	Formulations Research and Development
QC	Quality Control
AD	Analytical Development
HDPE	High Density Poly Ethylene
RH	Relative Humidity
°C	Degree Centigrade

8.0 FLOW CHART(s):

Not Applicable

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9.0 ANNEXURE(s):

Annexure No.	Details/Title of Annexure	Format No. (Current Version)
Annexure 01	Hold time Protocol	
Annexure 02	Recommended Hold time Data of different dosage forms.	
Annexure 03	Recording the observation during hold time study of tablets	
Annexure 04	Recording the observation during hold time study of Injectables	
Annexure 05	Recording the observation during hold time study of capsules	
Annexure 06	Recording the observation during hold time study of pellets	
Annexure 07	Recording the observation during hold time study of soft gelatin capsules	
Annexure 08	Recording the observation during hold time study of cream, ointments and gels	
Annexure 09	Recording the recommended hold time after completion of study with comments.	

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Annexure 01

Hold time Protocol

Objective:

Generic Name:		**Protocol No.:**	
Dosage Form:		**Mfg site:**	

Stages							
Qty stored							
Packing Details:							
Tests							
Performance trial							
Sampling Schedule							

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Annexure 02

Recommended Hold time Data of different dosage forms

1.0 Tablets:

S.No.	Stage	Tests	Proposed hold time*	Testing frequency	Proposed Sample qty*
1.	**Dry Mix material**	Assay & impurities	2 days	Initial, 1 day, 2 days, 3 days	250 g
2.	**Wet mass**	Microbial load Assay Impurities	--	Initial, 4 hrs., 8 hrs.	250 g
3.	**Lactose granules**	LOD Microbial load	12 months	Initial, 1 month, 2 months, 6 months, 9 months, 12 months, 15 months	2 kg
4.	**Lubricated granules**	Assay Impurities Moisture content Compressibility Particle size Distribution	5 days (3 days in case of sensitive molecule)	Initial, 15 days, 30 days	2 kg
5.	**Uncoated tablets**	Assay Impurities Disintegration time Dissolution profile Moisture content	30 days	Initial, 1 month, 2 months	250 g
6.	**Coated tablets**	Assay Impurities Disintegration time Dissolution profile Moisture content	30 days	Initial, 1 month, 3 months, 4 months	250 g
7.	**Coating solution**	Microbial load Weight per ml	2 days	Initial, 1 day, 3 days	250 ml

* Proposed hold time and sample quantities are given in general, it can be vary, based on the criticality of the molecule and formulation.

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2.0 Injectables

S.No.	Stage	Tests	Proposed hold time*	Testing frequency	Proposed Sample qty*
1.	Medicament Solution	Microbial load Assay Impurities pH Weight per ml	1 day	Initial, 24 hrs. 48 hrs.	250 ml
2.	Filtered Solution	Microbial load Assay Impurities pH Weight per ml	1 day	Initial, 24 hrs. 48 hrs.	250 ml

* Proposed hold time and sample quantities are given in general, it can be vary, based on the criticality of the molecule and formulation.

3.0 Capsules:

S.No.	Stage	Tests	Proposed hold time*	Testing frequency	Proposed Sample qty*
1.	Wet mass	Microbial load Assay Impurities	-----	Initial, 4 hrs, 8 hrs	250 g
2.	Lubricated granules	Assay Impurities Moisture content Particle size Distribution	5 days (3 days in case of sensitive molecule)	Initial , 15 days, 30 days	250 g
3.	Capsules	Assay Impurities Disintegration time Dissolution profile Moisture content	3 months	Initial , 1 m, 3m, 6 m	250 g

* Proposed hold time and sample quantities are given in general, it can be vary, based on the criticality of the molecule and formulation.

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4.0 Pellets:

S.No.	Stage	Tests	Proposed Hold time*	Testing frequency	Proposed Sample qty*
1.	Active	Assay Impurities	1 day	Initial, 1 day 2 days	100g
2.	Drug mixture blend	Assay Impurities	1 day	Initial, 2 days, 3 days	250 g
3.	Syrup solution	Microbial load Weight per ml	1 day	Initial, 1 day, 2 days	250 ml
4.	Wet pellets	Microbial load Assay Impurities	2 days	Initial, 2 days, 4 days	250 g
5.	Drug coated pellets	Assay Impurities	30 days	Initial, 30 days, 45 days	250 g
6.	Sub coating solution	Micorbial load Weight per ml	1 day	Initial, 1 day, 2 days	250 ml
7.	Sub coated pellets	Assay Impurities	30 days	Initial, 30 days, 45 days	250 g
8.	Enteric solution	Microbial load Weight per ml	1 day	Initial, 1 day, 2 days	250 ml
9.	Enteric coated pellets	Assay Impurities Dissolution profile	3 month	Initial, 1 m, 3 m, 6 m	250 g
10.	Capsules	Assay Impurities Dissolution profile	3 month	Initial, 1 m, 3 m, 6 m	250 g

* Proposed hold time and sample quantities are given in general, it can be vary, based on the criticality of the molecule and formulation.

5.0 Soft gelatin capsules

S.No.	Stage	Tests	Proposed hold time*	Testing frequency	Proposed Sample qty*
1.	Medicament	Microbial load Assay Impurities	1 day	Initial, 1 day, 2 days	250 g
2.	Capsules	Microbial load Assay Impurities Disintegration time	3 month	Initial, 1m, 3 m, 6 m	250 g

* Proposed hold time and sample quantities are given in general, it can be vary, based on the criticality of the molecule and formulation.

6.0 Creams, Ointments and Gels

S.No.	Stage	Tests	Proposed hold time*	Testing frequency	Proposed Sample qty*
1.	Medicament	Microbial load Assay Impurities Viscocity	12 hours	12 hrs, 24 hrs	250 g

* Proposed hold time and sample quantities are given in general, it can be vary, based on the criticality of the molecule and formulation.

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Annexure 03

Recording the observation during hold time study of tablets

Tablets

1. Dry Mix

Frequency	Test results		Comments
	Assay	Impurities	
Initial			
1 day			
2 days			
3 days			

2. Wet Mass

Frequency	Test results			Comments
	Microbial load	Assay	Impurities	
Initial				
4hrs				
8hrs				

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3. Lactose granules

Frequency	Test results		Comments
	LOD	Microbial load	
Initial			
1 month			
3 months			
6 months			
9 months			
12 months			
15 months			

4. Lubricated Granules

Frequency	Test results					Comments
	MC	Assay	Impurities	Compressibility	Particle size	
Initial						
15 days						
30 days						

5. Coating solution

Frequency	Test results		Comments
	Microbial load	Weight per ml	
Initial			
1 day			
3 days			

6. Uncoated tablets

Frequency	Test results					Comments
	MC	Assay	Impurities	DT	Dissolution profile	
Initial						
1 month						
2 months						

7. Coated tablets

Frequency	Test results					Comments
	MC	Assay	Impurities	DT	Dissolution profile	
Initial						
1 month						
3 months						
4 months						

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Annexure 04

Recording the observation during Hold Time Study of Injectables

Injectables

1.0 Medicament solution

Frequency	Test results					Comments
	pH	Assay	Impurities	Weight per ml	Microbial load	
Initial						
24 hrs						
48 hrs						

2.0 Filtered solution

Frequency	Test results					Comments
	pH	Assay	Impurities	Weight per ml	Microbial load	
Initial						
24 hrs						
48 hrs						

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Annexure 05

Recording the observation during hold time study of Capsules

Capsules

1. Wet Mass

Frequency	Test results			Comments
	Microbial load	Assay	Impurities	
Initial				
4hrs				
8hrs				

2. Lubricated Granules

Frequency	Test results					Comments
	MC	Assay	Impurities	Compressibility	Particle size	
Initial						
15 days						
30 days						

3. Capsules

Frequency	Test results					Comments
	MC	Assay	Impurities	DT	Dissolution profile	
Initial						
1 Month						
2 Months						
6 Months						

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Annexure 06

Recording the observation during Hold Time study of Pellets

Pellets

1. Active

Frequency	Test results		Comments
	Assay	Impurities	
Initial			
1 day			
2 days			

2. Drug mixture blend

Frequency	Test results		Comments
	Assay	Impurities	
Initial			
2 days			
3 days			

3. Syrup solution

Frequency	Test results		Comments
	Microbial load	Weight per ml	
Initial			
1 day			
2 days			

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4. Wet Pellets

Frequency	Test results			Comments
	Microbial load	Assay	Impurities	
Initial				
2 days				
4 days				

5. Drug coated pellets

Frequency	Test results		Comments
	Assay	Impurities	
Initial			
30 days			
45 days			

6. Sub coating solution

Frequency	Test results		Comments
	Microbial load	Weight per ml	
Initial			
1 day			
2 days			

7. Sub coated pellets

Frequency	Test results		Comments
	Assay	Impurities	
Initial			
30 days			
45 days			

8. Enteric solution

Frequency	Test results		Comments
	Microbial load	Weight per ml	
Initial			
1 day			
2 days			

9. Enteric coated pellets

Frequency	Test results			Comments
	Assay	Impurities	Dissolution profile	
Initial				
1 month				
3 months				
6 months				

10. Capsules

Frequency	Test results			Comments
	Assay	Impurities	Dissolution profile	
Initial				
1 month				
3 months				
6 months				

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Annexure 07
Recording the observation during hold time study of Soft Gelatin capsules
Soft gelatin capsules

1.0 Medicament

Frequency	Test results			Comments
	Assay	Impurities	Microbial load	
Initial				
1 day				
2 days				

2.0 Capsules

Frequency	Test results				Comments
	Assay	Impurities	Microbial load	DT	
Initial					
1 Month					
3 Months					
6 Months					

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Annexure 08

Observation during Hold Time study of Cream Ointments & Gels

Creams, Ointments & Gels

1.0 Bulk

Frequency	Test results				Comments
	Assay	Impurities	Microbial load	Viscosity	
Initial					
2 wks					
4 wks					

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Annexure 09

Recording the recommended hold time after completion of study with comments

Name of the product:

S.No.	Stage	Recommended hold time

Comments: