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Hold Time Stability Studies in Pharmaceutical Industry: Review

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Abstract

Stability studies are playing main role in the pharmaceutical industry. Stability studies for pharmaceutical drug products are having all guidelines like ICH, USFDA, EMEA, WHO and etc. Hold time study data shall give the assurance the maximum allowable hold times for bulk and in-process drug products. Generally one lot can be used for validating hold times if any inconsistency results were observed then another two lots can be used for this study. Major hold study required stages are mixing, blending, lubrication, binder solution, coating solution, uncoated tablets, coated tablets, filled capsules, syrup solution, power for injection, liquid injection, bulk creams/ointments/gels. Hold study samples need to pack with the regular used poly ethylene bags, sterilized containers, HDPE or Glass containers. Hold samples need to store at GMP conditions i.e. where the lot or stage holds in the manufacturing area. All the regulatory agencies also may expect the hold time study at critical stages to understand the trend of degradation during holding at in-process stages.

Keywords: Hold time stability; Hold time study time intervals; Pharmaceutical drug products; Dosage forms; USFDA and EU

Introduction

Pharmaceutical drug products stability studies are important for establishing the shelf life of the products. Stability studies can be performed for finished drug substances and drug products with the real time, intermediate and accelerated storage conditions. All stability study guidelines are mentioned in ICH, FDA, EMEA and WHO guidelines.

Hold time study data shall give the assurance the maximum allowable hold times for bulk and in-process drug products [1]. Generally one lot can be used for validating hold times if any inconsistency results were observed then another two lots can be used for this study. Although there are no specific regulations or guidance documents on bulk product hold times, GMP dictates that hold times should be validated to ensure that in-process and bulk product can be held, pending the next processing step, without any adverse effect to the quality of the material. Hold time study provides the re-assurance of the quality at each in-process stages.

Hold Time Stability Study

It is a stability establishment tool for each and every stage in the drug product manufacturing. In the drug product development, hold time stability is an important tool for establishing the in-process hold time. Hold time stability is evaluating for each stage in the product manufacturing. Hold stability study can demonstrates how much time is suitable for hold the blend or bulk stage before processing to the next stage. When appropriate, time limits for the completion of each phase of production shall be established to assure the quality of the drug product.

Hold time stability results should meet the product specifications. Hold time study shall be carried out with the storage container packing's only. If the dosage form is stored in bulk containers for over 30 days, real-time stability data under specified conditions should be generated to demonstrate comparable stability to the dosage form in the marketed package [2].

Hold Time Stability Study Flow in the Pharmaceutical Industry

Hold time studies are performing during the product development, i.e scale up stage and commercial validation stages. Before starting the hold study, formulation scientist needs to select the critical stages (where the study is required), time points and tests. The flow of hold study has represented in the (Figure 1). In the pharmaceutical industry the hold study can be carried with the following steps. i. Selection of critical steps; ii. Hold study time points and tests; iii. Hold study protocol; iv. Hold study analysis; v. Hold study report and vi. Hold study results evaluation.

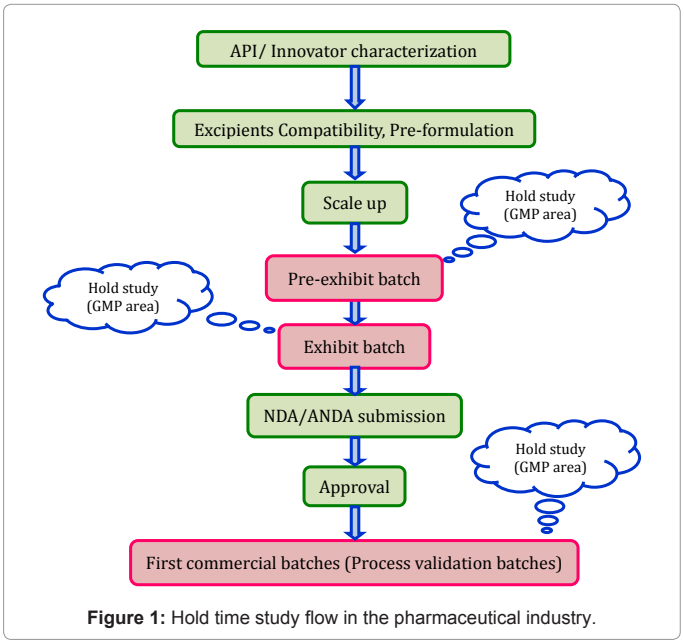

Figure 1: Hold time study flow in the pharmaceutical industry.

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Hold Study Stages

The selection of hold time stability study conditions is very important for starting the hold study. These conditions are same with the manufacturing area/hold area conditions, so these conditions are may vary with the product to product. Based on the manufacturing process of the dosage forms hold study stages can be decided. Hold study required stages are summarized in the table 1. All pharmaceutical dosage forms hold study stages and study time requirements are discussed in detail like tablets, capsules, liquids, semi solids and injections.

Tablets

Hold studies can be proceeded in tablets are based on the manufacturing process. Generally tablets are two types i.e. 1. Un-coated and 2. Coated tablets (film coating or enteric coating). Both un-coated and coated tablets are manufacturing with direct compression, dry granulation or wet granulation methods so each manufacturing process have different stages. Based on the manufacturing process the hold time stability study can be decided.

Un-coated tablets

Un-coated tablets are manufacturing with direct compression method and wet granulation methods. Direct compression method is the uncomplicated and cost effective method for the manufacturing of tablets because it requires less processing stages than other techniques such as wet granulation and roller compaction. Most API's can't be compressed directly into desired tablets due to lack of flow, cohesion properties and lubrication.

Direct compression/Dry granulation: This category of tablets are manufacturing with the following steps i.e. dispensing, sifting, dry mixing/roll compaction, blending, compression and packing. Hold

Dosages form	Hold study required stages
 Tablets	1. Blending 2. Dry mixing 3. Binder solution 4. Roll compaction 5. Un-coated tablets 6. Coated tablets 7. Wet granules 8. Coating solution
 **Capsules**	1. Blending powder 2. Filled capsules 3. Binder solution 4. Pellets 5. Dry granulation sample 6. Wet granulation sample 7. Coated pellets 8. Un-coated pellets 9. MUFS tablets
 **Liquids**	1. Un-filtered solution 2. Filtered solution 3. Sugar solution 4. Before pH adjustment stage 5. After pH adjustment stage
 **Semi solids**	1. Bulk sample 2. Before pH adjustment stage 3. After pH adjustment stage
   **Injectable**	1. Final solution 2. Water for injection sample 3. Lyophilized sample 4. Before pH adjustment stage 5. After pH adjustment stage

Table 1: Hold stages in all type of dosage forms.

study required for this formulation is Dry mixing, roll compaction, blending and un-coated tablets. The required tests and time points are listed in the (Table 2) and flow chart, hold study requirements are represented in (Figure 2).

Wet granulation: Wet granulation procedure is involves the addition of a liquid solution (with or without binder) to powders, to form a wet mass or it forms granules by adding the powder together with an adhesive. It improves flow property and compression

Hold study required	Hold study time points	Tests required*
Un-Coated Tablets (Direct Compression/ Dry Granulation)		
Blending	7, 15, 30, 45 and 60days	Description, LOD or water content and Assay
Lubrication	7, 15, 30, 45 and 60days	Description and LOD or water content and assay.
Un-coated tablets	7, 15, 30, 45 and 60days	Description, LOD or water content, assay and dissolution.
Un-Coated Tablets (Wet Granlulation)		
Dry mixing	7, 15 and 30days	Description, LOD or water content.
Binder solution	Initial, 12, 24, 36, 48 and 72 hours	Description
Wet granules	Initial, 12, 24, 36, 48 and 72 hours	Description, LOD or water content and assay, Micro-bails limits
Blending	7, 15, 30, 45 and 60days	Description, LOD or water content and assay.
Un-coated tablets	7, 15, 30, 45 and 60days	Description, LOD or water content, assay and dissolution.
Coated Tablets (Direct Compression/ Dry Granulation)		
Pre-Blending	7, 15, 30, 45 and 60days	Description, LOD or water content.
Lubrication	7, 15, 30, 45 and 60days	Description, LOD or water content, and assay.
Un-coated tablets	7, 15 and 30, 45 and 60days	Description, LOD or water content, assay and dissolution.
Coating solution	Initial, 12, 24, 36, 48 and 72 hours	Description
Coated tablets	7, 15 and 30, 45 and 60days	Description, LOD or water content, assay and dissolution.
Coated Tablets (Wet Granulation)		
Binder solution	Initial, 12, 24, 36, 48 and 72 hours	Description, LOD or water content, and assay.
Wet granules	Initial, 12, 24, 36, 48 and 72 hours	Description, LOD or water content, and assay.
Blending	7, 15, 30, 45 and 60days	Description, LOD or water content and assay.
Un-coated tablets	7, 15, 30, 45 and 60days	Description and LOD or water content, dissolution and assay.
Coating solution	Initial, 12, 24, 36, 48 and 72 hours	Description.
Coated tablets	7, 15, 30, 45 and 60days	Description, LOD or water content, assay and dissolution.
Dispersible/ Orally Disintegrating Tablets		
Blending	7, 15 and 30, 45 and 60days	Description, LOD or water content, and assay.
Compressed tablets	7, 15 and 30, 45 and 60days	Description, LOD or water content, assay and dissolution.
Capsules (Power Filling)		
Mixing	7, 15 and 30, 45 and 60days	Description, LOD or water content and assay.
Lubrication	Initial, 12, 24, 36, 48 and 72 hours	Description and assay.
Filled capsules	7, 15 and 30, 45 and 60days	Description, LOD or water content, assay and dissolution.
Capsules (Wet Granules Filled)		
Dry mixing	7, 15, 30, 45 and 60days	Description and LOD or water content and assay.
Binder solution	Initial, 12, 24, 36, 48 and 72 hours	Description
Wet granulation samples	7, 15, 30, 45 and 60days	Description and LOD or water content and assay.
Blending	7, 15, 30, 45 and 60days	Description and LOD or water content and assay.
Filled capsules	7, 15, 30, 45 and 60days	Description and LOD or water content and assay.
Capsules (Pellets Filled or Mups)		
Drug Pellets	7, 15 and 30days	Description and assay.
Coating solution	Initial, 12, 24, 36, 48 and 72 hours	Description
Coated pellets	7, 15 and 30days	Description, LOD or water content and assay
Blending	7, 15, 30, 45 and 60days	Description and LOD or water content and assay.
Filled capsules	7, 15, 30, 45 and 60days	Description, LOD or water content, assay and dissolution.
Un-coated tablets (MUPS)	7, 15, 30, 45 and 60days	Description, LOD or water content, assay and dissolution.
Coated tablets (MUPS)	7, 15, 30, 45 and 60days	Description, LOD or water content, assay and dissolution.
Liquids (Syrups, Oral Solutions, Suspensions and Linctus)		
Un-filtered solution	1, 2, 5 and 7days	Description, pH value, wt. per mL and assay
Filtered solution	1, 2, 5 and 7days	Description, pH value, wt. per mL and assay
Suspensions (Powders)		
Blend powder	7, 15, 30, 45 and 60days	Description and LOD or water content and assay.
Re-constituted solution	Initial, 12, 24, 36, 48 and 72 hours	Description, pH value, wt. per mL and assay
Injections (Liquids-Terminally Sterilized)		
Sterilized bottles or vials	1, 3 and 7days	Sterility/ Bio burden
Filtered liquid	24, 48, 72hours	Sterility/ Bio burden, Assay, PH
Sterilized product	24, 48, 72hours	Sterility/ Bio burden, Assay ,PH
Injections (Lyophilized)		

Sterilized bottles or vials	1, 3 and 7days	Sterility/ Bio burden, Assay, PH
Mixing	24, 48, 72hours	Sterility/ Bio burden, Assay, PH
Lyophilized	24, 48, 72hours	Sterility/ Bio burden, Assay, PH
Injection (Powder for Injection)		
Vials sterilization	1, 3 and 7days	Sterility/ Bio burden
Filling	24, 48, 72hours	Sterility/ Bio burden, Assay, PH
Ointments/ Gels/ Creams		
Bulk stage	Initial, 12, 24, 36, 48 and 72 hours	Description, pH value, wt. per mL and assay

*these tests may vary depend on the requirement.

Table 2: Hold time study requirements for all types of dosage forms.

characteristics and increases density of granules, reduction of dust hazardous, increase the color distribution. Hold study required stages are dry mixing, wet granulation, binder solution, blending and un-coated tablets. The details of manufacturing process and hold study details are represented in (Figure 3 and Table 2) [3].

Coated tablets

Coated tablets are tablets covered with one or more layers of mixtures of various substances such as natural or synthetic resins, gums, gelatin, inactive and insoluble fillers, sugars, plasticizers, polyols, waxes, coloring matter authorized by the competent authority and sometimes flavoring substances and active substances. The substances used as coatings are usually applied as a solution or suspension in conditions in which evaporation of the vehicle occurs. This class of tablets also manufactured with direct compression/dry granulation and wet granulation procedures. Direct compression/dry granulation method tablets manufacturing process and hold time stability requirements are represented in (Figure 3). Wet granulation manufacturing process and hold study requirements represented in (Figure 4).

Dispersible Tablets/Orally disintegrating tablets (ODT)

Dispersible tablets are typically dispersed in water or another liquid before they are administered to the patient. This drug product is for patients having difficulties in swallowing solid dosage forms like tablets or capsules. ODTs can be taken without water – a benefit for "dry" situations where water or other liquid drinks are not available. A pleasant taste is achievable with appropriate taste-masking and flavoring, which is most often a mandatory requirement for such drug products [4]. The micro pellet dosage form concept easily allows the combination of the taste masking approach with a modified drug release approach. Therefore, dispersible tablets and ODT formulations can be applied for both immediate release and for modified release products. Manufacturing process and hold study requirements represented in (Table 2 and Figures 2-6).

Capsules

Capsules are widely used as a highly flexible drug product vehicle. Capsules can be filled with powders, granules, pellets, tablets, mini-tablets, etc. The two main types of capsules are available 1. Hard-shelled capsules, which are normally used for dry, powdered ingredients or miniature pellets; 2. Soft-shelled capsules, primarily used for oils and for active ingredients that are dissolved or suspended in oil. Manufacturing process and hold study requirements of all types for capsules are represented in (Table 2 and Figures 7-9).

Suspensions

Suspension dosage form is a preferred and widely accepted dosage forms for insoluble or poorly soluble drugs for various therapeutic applications. The suspension dosage form has long been used for insoluble and poorly soluble drugs for making oral, topical and parenteral products.

Development of stable suspensions over the shelf life of the drug product continues to be a challenge on many fronts. A good understanding of the fundamentals of disperse systems is essential in the development of a suitable pharmaceutical suspension. The development of a suspension dosage form follows a very complicated path. The selection of the proper excipients (surfactants, viscosity imparting agents, etc.) is important. The particle size distribution in the finished drug product dosage form is a critical parameter that significantly impacts the bioavailability and pharmacokinetics of the product. Appropriate analytical methodologies and instruments (chromatographs, viscometers, particle size analyzers, etc.) must be utilized to properly characterize the suspension formulation. (Figures 10-16).

Fixed Dose Combinations

Fixed dose combination drug products contain more than one API in a fixed dose, allowing the patient to reduce the number of drug products to be taken. Improved patient compliance is the fundamental purpose of the fixed dose combination concept. Different APIs (e.g.

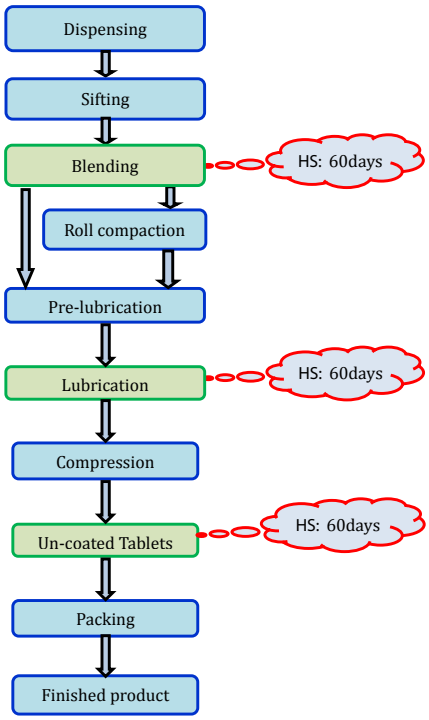

Figure 2: Un-coated tablets (direct compression/ dry granulation) manufacturing process and hold time study requirements.

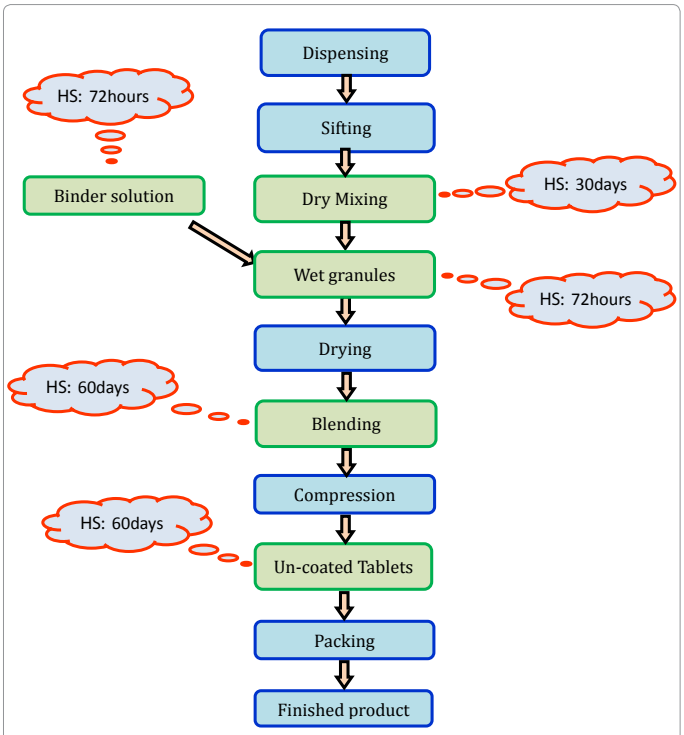

Figure 3: Un-coated tablets (wet granulation) manufacturing process and hold time study requirements.

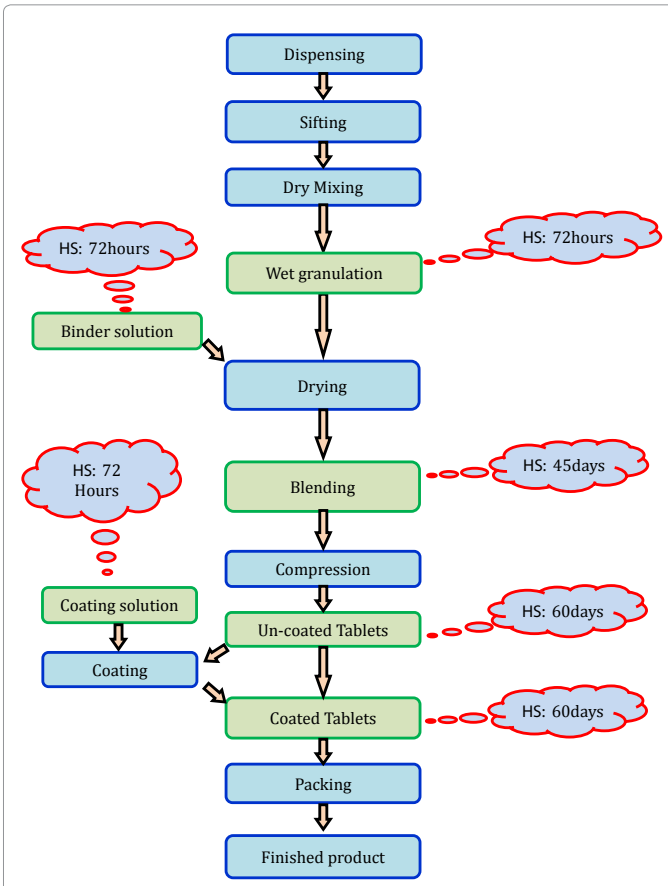

Figure 4: Coated tablets (wet granulation) manufacturing process and hold time study requirements.

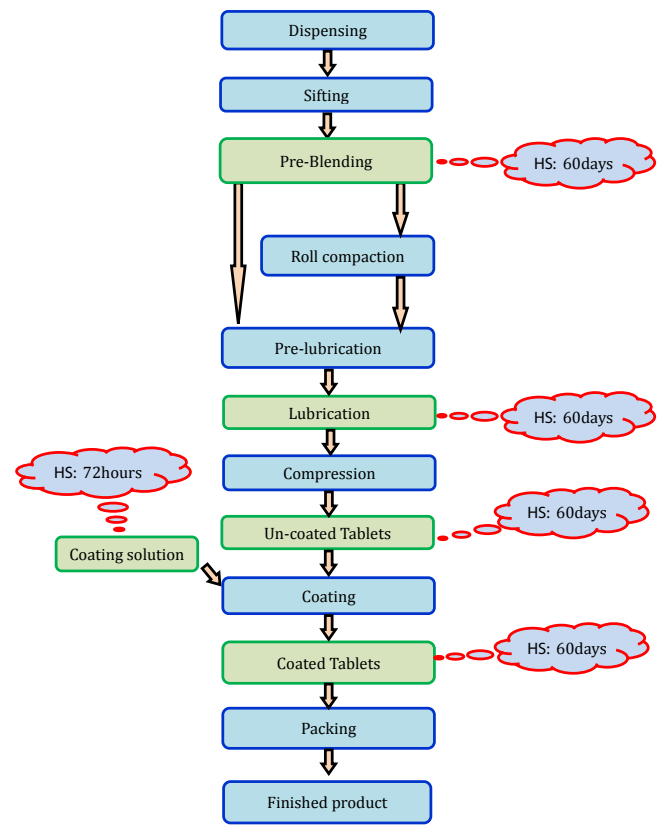

Figure 5: Coated tablets (direct compression/ dry granulation) manufacturing process and hold time study requirements.

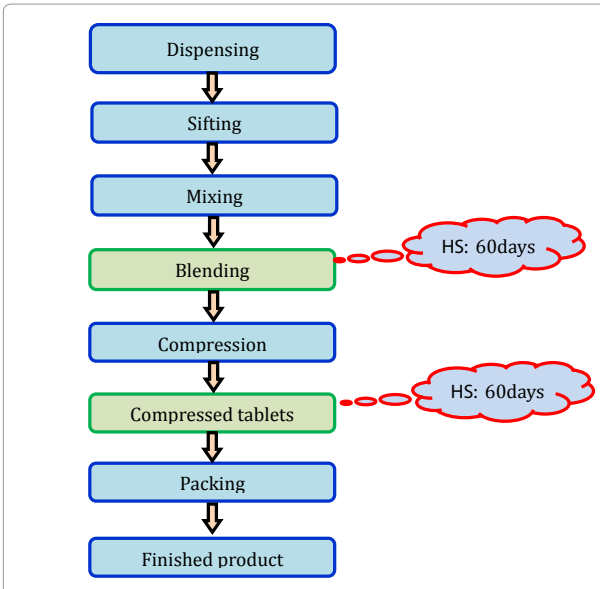

Figure 6: Dispersible/ Orally disintegrating tablets manufacturing process and hold time study requirements.

in the form of granules, pellets, micro-pellets) can be processed into tablets, capsules, stick packs, sachets, etc.

Hold Study Time Points and Tests

The selection of hold study stages are important for the evaluation

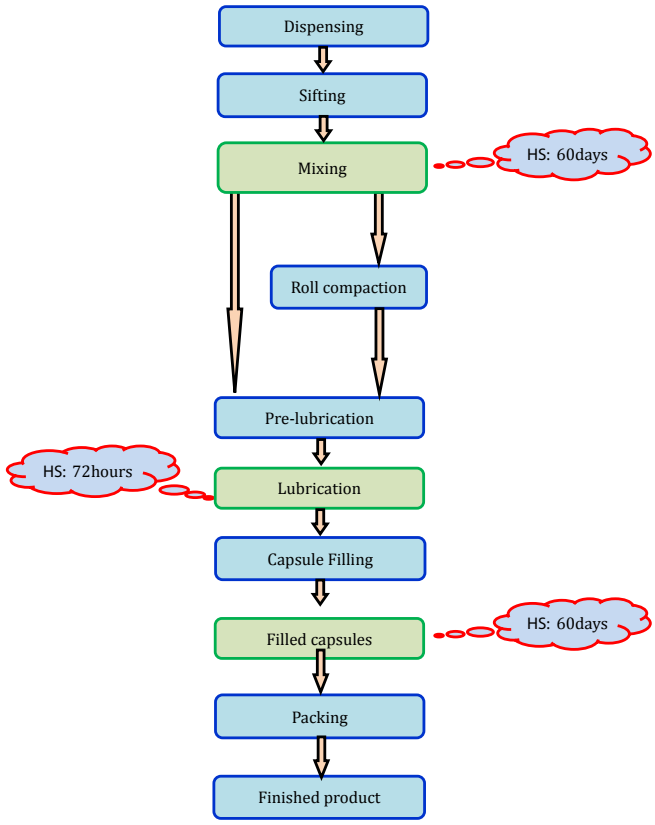

Figure 7: Capsules (powder filling) manufacturing process and hold time study requirements.

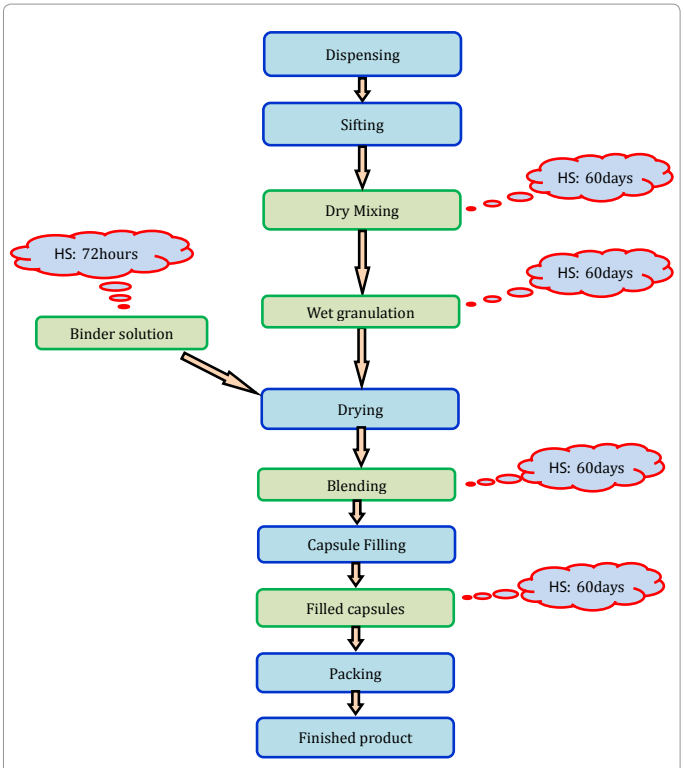

Figure 8: Capsules (wet granulation) manufacturing process and hold time study requirements.

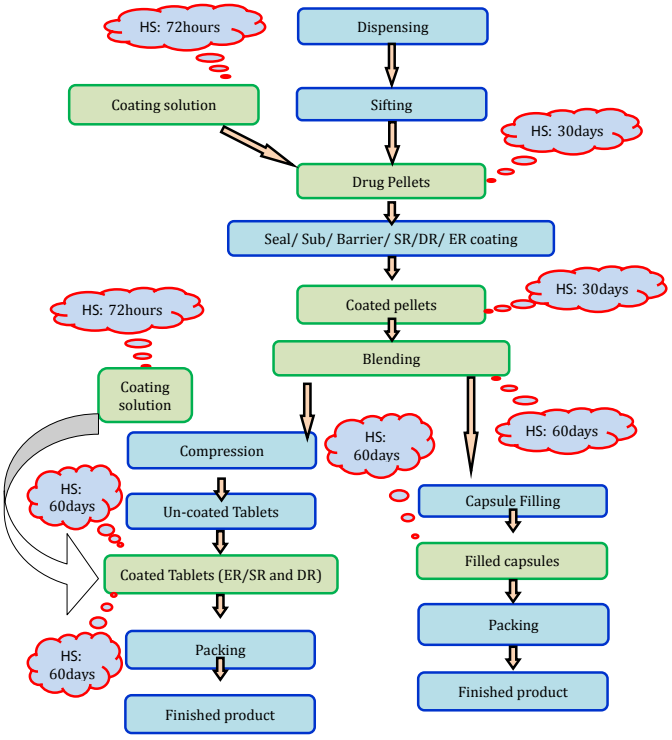

Figure 9: Capsules (pellets/MUPS) manufacturing process and hold time study requirements.

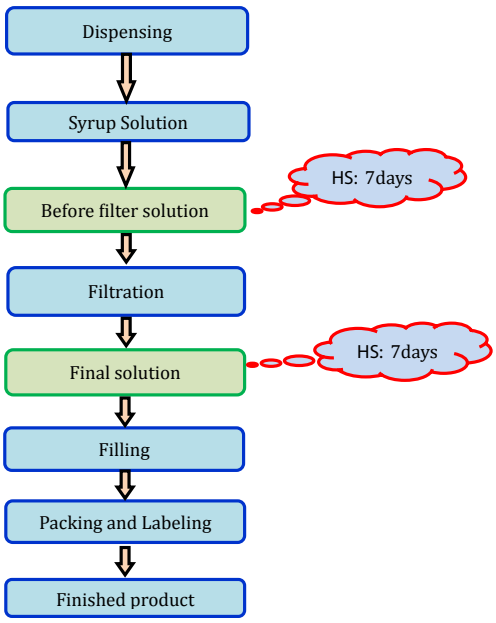

Figure 10: Liquid syrups manufacturing process and hold time study requirements.

of hold study, after selecting the stage then time points and tests need to select. Hold study time points are generally

Hours: 1, 3, 5, 7, 12, 24, 36, 48, 72 hours

Days: 1, 7, 15, 30, 45, 60, 75, 90 days

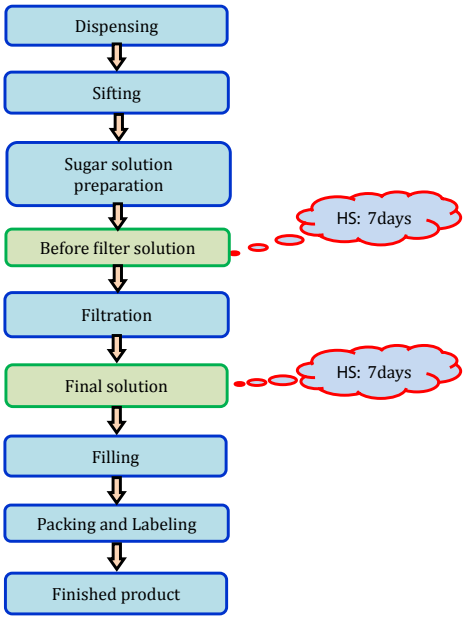

Figure 11: Syrups/ Oral solutions manufacturing process and hold time study requirements.

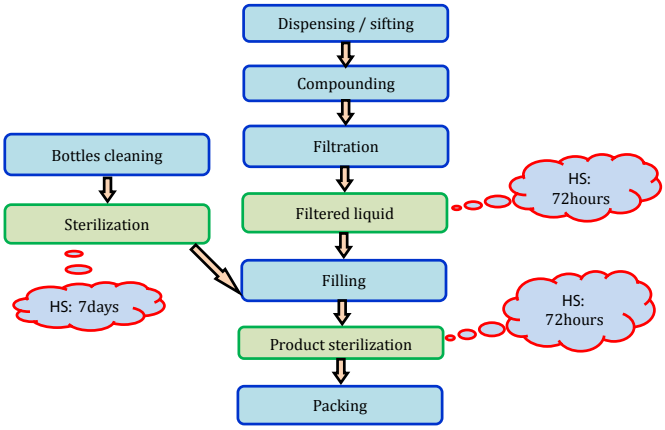

Figure 12: Injectable (Liquid-Terminally sterilized) manufacturing process and hold time study requirements.

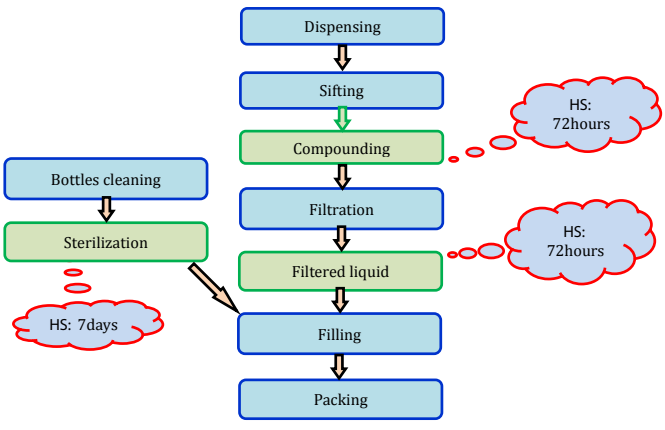

Figure 13: Injectable (Liquid) manufacturing process and hold time study requirements.

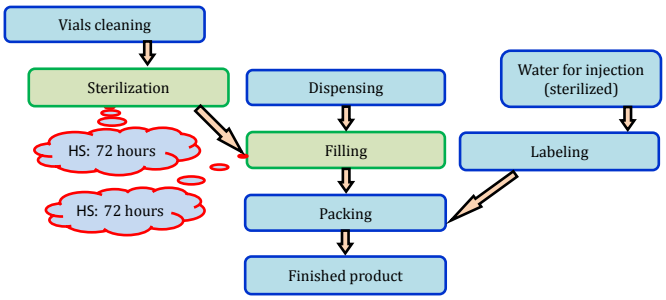

Figure 14: Injectable (Powder for injection) manufacturing process and hold time study requirements.

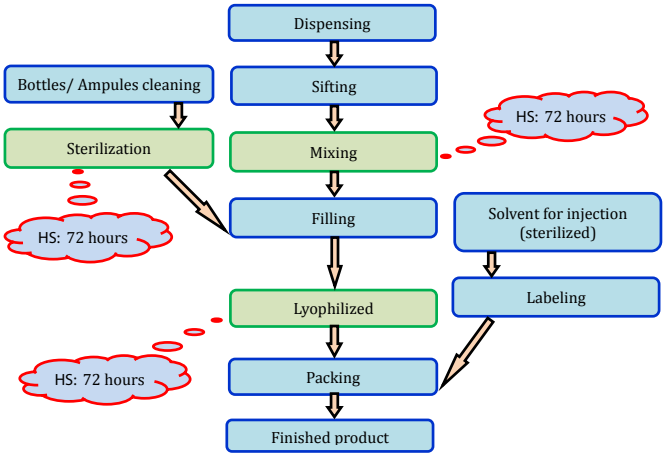

Figure 15: Injectable (Lyophilized) manufacturing process and hold time study requirements.

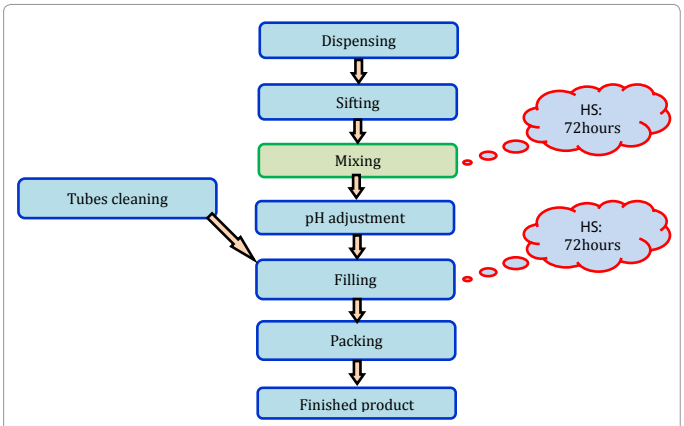

Figure 16: Ointments/ Gels/ Creams manufacturing process and hold time study requirements.

Hold stages, time points and required test for all dosage forms are represented in (Table 2) [5].

Hold Time Study Protocol

Hold time study protocol can be prepared on the basis of product manufacturing process of the drug product. The main contents in the protocol are, hold study stages, study time points and analytical tests.

Hold Time Study Results Evaluation

Each manufacturing stage shelf life can be determined based on the

Hold study Stage	Hold study time points passed	Proposed shelf life
Dry mixing/ Roll compaction	7, 15 and 30 days	Description, LOD or water content and assay.
Coating solution	Initial, 12, 24, 36, 48 and 72 hours	Description
Lubricating solution	Initial, 12, 24, 36, 48 and 72 hours	Description
Un-coated tablets	Initial, 7, 15 and 30, 45 and 60days	Description, LOD or water content, assay and dissolution.
Coated tablets	Initial, 7, 15 and 30, 45 and 60days	Description, LOD or water content, assay and dissolution.
Filled capsules	Initial, 7, 15 and 30, 45 and 60days	Description, LOD or water content, assay and dissolution.
Un-filtered solution	Initial, 12, 24, 36, 48 and 72 hours	Description, pH value, wt. per mL and assay
Filtered solution	Initial, 12, 24, 36, 48 and 72 hours	Description, pH value, wt. per mL and assay
Final solution (injection)	Initial, 12, 24, 36, 48 and 72 hours	Description, pH value, wt. per mL and assay
Final powder (injection)	Initial, 12, 24, 36, 48 and 72 hours	Description and assay
Final Lyophilized sample (injection)	Initial, 12, 24, 36, 48 and 72 hours	Description, pH value, wt. per mL and assay
Bulk sample (semi solids)	Initial, 12, 24, 36, 48 and 72 hours	Description, pH value, wt. per mL and assay
Final sample (Ointments, Gels, Creams)	Initial, 12, 24, 36, 48 and 72 hours	Description, pH value, wt. per mL and assay
Un-coated pellets (capsules)	Initial, 7, 15 and 30, 45 and 60days	Description, LOD or water content, assay and dissolution.
Coated pellets (capsules)	Initial, 7, 15 and 30, 45 and 60days	Description, LOD or water content, assay and dissolution.

Table 3: Hold time study time points and shelf life considerations.

hold study results. If the hold time samples are passing at 60 days time point then the shelf life of the particular stage can be considered up to 45 days. All hold study time points and shelf life considerations were represented in table 3.

Recommendations and Conclusion

Hold study evaluation plays a main role for manufacturing the new products in GMP conditions. Based on the hold time study establishment and shelf life product manufacturing plan can be decided. Hold time study results are passing the 60 days time interval then 45 days limit is good for general practice. In the same way if the stage is passing the 72 hours interval then 48 hours limit is general practice. If not performed the hold study in the product development stage then in commercial level need to perform the hold study for first three commercial batches [6,7].

Disclaimer

The purpose of this hold time study review is solely educational. This review article is built from authors work and experience.

References

1. Ali H, Khatri AM, Modi AR, Patel A (2011) Standard Practice of sampling, storage and hold time for pharmaceutical tablet and injection during manufacturing process, Drug Invention Today 3: 157-159.
2. Forsyth RJ (2008) Equipment Hold-Time for Cleaning Validation. Pharm technol.
3. QC Bulk Pharmaceuticals Work Group (1995) PhRMA Guidelines for the Production, Packing, Repacking or Hold of Drug Substances. Quality Steering Committee, PhRMA Science and Regulatory Section, Part I and Part II, Pharmaceutical Technology.
4. European Medicines Agency (2010) Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials. Committee for Medicinal Products for Human Use, London, United Kingdom.
5. Lee AS, Chou JH (2009) Case Studies for Stability of In-Process Pools. Genentech, Inc.
6. U.S. Department of Health and Human Services (2010) Guidance for Industry Drug Substance Chemistry, Manufacturing and Controls Information.
7. In-Process and Bulk Drug Product Holding Times.