



STUDY OF STABILITY AND LABELING REQUIREMENTS OF INHALATION AND NASAL PRODUCT IN US AND EUROPE

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Article Received on 18/02/2015

Article Revised on 11/03/2015

Article Accepted on 02/04/2015

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ABSTRACT

Inhalation and Nasal products are used in the Asthma and COPD so it requires precise regulation. Stability studies ensure the maintenance of product quality throughout the shelf life that is pre-requisite for the acceptance and approval of Inhalation and Nasal product. Stability studies play an important role in Inhalation development, possibly more than other delivery systems. These studies are required to conduct

in a planned approach following the rules issued by ICH. Labeling is essential for any pharmaceutical product as it gives all the detail about the product which will be benefit for patient. Label facilitate manufacturer to market their product and catch people's attention. It is useful to Consumer additionally to allow them distinguish the product form one another. In this article Stability studies which are required for Inhalation and Nasal product are same for both the countries. By studying the stability guideline we can easily find out the shelf life of the product and it is necessary for pharmaceutical companies to file their product in US and Europe. And labeling requirement which is essential for Inhalation and Nasal product are given in both the countries.

KEYWORDS: Stability Requirements, labeling, Stability studies, ICH, Inhalation and Nasal product.

INTRODUCTION^[1]

Stability is an ability of a substance to remain unchanged over the time under stated or reasonably expected condition of storage and use. Usually condition that may cause instability such as humidity, temperature, and shock.

Stability studies play an important role in Inhalation drug development. As drug Inhalation is growing in popularity for local and systemic therapies, laboratory testing of Inhaled products is becoming increasingly valuable in determining their safety and efficacy. The size distribution of the delivered formulation and the delivery of the drug from the device are affected by the chemical stability of the active drugs, and the effect of temperature and humidity.

Measurement of particle/droplet size throughout a stability study is important For Nebulizers, pressurized metered-dose inhalers (pMDIs), and dry-powder inhalers (DPIs), as in addition to maintain the target area of the delivery, it can also regulate the rate of dissolution and bioavailability at the target site.

During early formulation development, accelerated feasibility studies should be designed to determine any potential excipient compatibility issues which can be identified quickly.

Stability testing provides essential data on how the quality of a pharmaceutical varies over time under the influence of different environmental factors such as temperature, humidity and photo-stability.

ICH stability services include long-term stability, accelerated stability, photo-stability, comparative stability and forced degradation storage and analytical studies.

Storage Stability Conditions

- 21°C / 45% RH
- 25°C / 40% RH, 25°C / 60% RH
- 30°C / 60% RH, 30°C / 65% RH and 30°C / 70% RH
- 40°C / 20% RH, 40°C / 25% RH, 40°C / 75% RH
- 50°C / 75% RH
- 50°C, 60°C and 80°C uncontrolled humidity
- 2-8°C, -20°C, -40°C and -80°C storage capacity
- Photo-stability (ICH Options 1 & 2)

- Specialized conditions
- Temperature cycling.

STABILITY REQUIREMENTS^[2]

The General stability requirement of US and Europe is given below:

General: The design of the formal stability studies for the drug product should be based on

- knowledge of the behavior and properties of the drug substance,
- Experience gained from clinical formulation studies.

Photo stability Testing: In this test one primary batch of the drug product should be used and standard conditions according to ICH Q1B should be maintained.

Selection of Batches

- It should requires at least three primary batches;
- Two of the three batches should be at least pilot scale batches
- Drug product should be manufactured by using different batches of the drug substance. Stability studies should be performed on each individual strength and container size of the drug product.

Container Closure System: Stability testing should be conducted on the dosage form packaged in the container closure system proposed for marketing.

Information on result of open storage stress condition and studies in other packaging material should be included. Stability testing should be conducted on the dosage form packaged in the container closure.

Specification: Stability studies should include the list of test and test attributes include testing of those attributes of the drug substance that are susceptible to change during storage and are likely to influence quality, safety, and/or efficacy. The testing should the physical, chemical, biological, and microbiological attributes.

Testing Frequency

For Long-term studies: The frequency of testing at the long-term storage condition should normally be every 3 months over the first year, every 6 months over the second year, and annually thereafter through the proposed shelf life.

Accelerated studies: General minimum of three time points, including the initial and final time points (e.g., 0, 3, and 6 months).

Intermediate storage condition: When testing at the intermediate storage condition, a minimum of four time points, including the initial and final time points (e.g., 0, 6, 9, 12 months), from a 12-month study is suggested.

Reduced design: Matrixing or bracketing for reduction of testing frequency if justified.

Storage Conditions

The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment, and subsequent use. Long term testing should cover at least 12 months.

Data from the accelerated storage condition and, if appropriate, from the intermediate storage condition can be used to evaluate the effect of short-term excursions outside the label storage conditions.

Long-term, accelerated, and, where appropriate, intermediate storage conditions for drug substances are detailed in the sections below:

Table 1: General storage condition

Study	Storage condition	Minimum time period covered by data at submission
Long-term*	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH	12 months
Intermediate**	30°C ± 2°C/65% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months

* It is up to the applicant to decide whether long-term stability studies are performed at 25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH.

** If 30°C ± 2°C/65% RH ± 5% RH is the long-term condition, there is no intermediate condition.

Table 2: Drug substances intended for storage in a refrigerator

Study	Storage condition	Minimum time period covered by data at submission
Long-term	5°C ± 3°C	12 months
Accelerated	25°C ± 2°C/60% RH ± 5% RH	6 months

- If significant change between 3 and 6 months at 25°C/60% shelf life based on real time data
- If significant change within 3 months, discussion about short term excursions outside label storage.
- As possible support one batch shorter than 3 months and more frequent testing.

Table 3: Drug substances intended for storage in a freezer

Study	Storage condition	Minimum time period covered by data at submission
Long-term	-20°C ± 5°C	12 months

Shelf life based on real time data testing on a single batch at 5°C for appropriate time period

Drug products in impermeable container: Studies can be conducted under any controlled or ambient humidity condition.

Drug products in semi-permeable container: Evaluation for potential water loss for aqueous-based products in semi-permeable Containers and Evaluation under condition of low relative humidity.

Table 4: storage condition in semi-permeable container

Study	Storage condition	Minimum time period at submission
Long term *	25°C ± 2°C/40% ± 5% or 30°C ± 2°C/35% ± 5%	12 months
Intermediate**	30°C ± 2°C/35% ± 5%	6 months
Accelerated	40°C ± 2°C/not more than 25%	6 months
Accelerated	40°C ± 2°C/75% ± 5%	6 months

*It is up to the applicant, to decide whether long term stability is performed at 25°C ± 2°C/60% ± 5% or 30°C ± 2°C/65% ± 5%.

** If 30°C ± 2°C/65% ± 5% is the long-term condition, there is no intermediate condition

Stability Commitment

When proposed shelf life not covered: When long term stability data do not cover proposed shelf life granted at time of Approval commitment should be made to continue post approval to establish the shelf life.

Commitment not necessary: Submission includes data on three production batches covering proposed shelf life

Commitment required: Submission includes data from 3 production batches, commitment to continue through proposed shelf life

- Fewer than three production batches commitment continue with these studies through proposed shelf life and place additional production batches to a total of three on long term and accelerated stability testing through proposed shelf life.
- No Production batches commitment to place first three production batches on long term and accelerated stability testing through proposed shelf life.

Evaluation

Stability information includes Systematic approach in presentation and evaluation of stability information should include results from physical, chemical, biological and microbiological tests.

Purpose of stability studies is to establish shelf life and storage instructions applicable for all further batches manufactured and packed under similar circumstances. Any evaluation should cover not only the assay, but also the levels of degradation products and other appropriate attributes.

Formal statistical analyses includes for quantitative attributes which change with time determination of time at which the 95% one sided confidence limit for the mean curve intersects the acceptance criteria. Data of batches can be combined if batch to batch variability is small:

- slope of regression line
- zero time intercepts

Statements/Labeling

Storage Statement

Storage statement for labeling should be in accordance with national/regional requirements based on the stability evaluation. It should be direct link between label storage statement and demonstrated stability. The statement should be based on the stability evaluation of the drug substance. Expiration date should be displayed on container label.

Table 5: Stability test required for Inhalation and Nasal products: ^[3,4]

Metered Dose Inhaler & Nasal Aerosol	Inhalation solution & powder	Nasal Sprays (solution & suspension)
Appearance	Appearance	Appearance
Color	Color	Color
Assay	Assay	Assay
Degradation product	Degradation product	Degradation product
Dose content uniformity	pH	Clarity
Labeled number of actuation	Sterility	Preservative
Aerodynamic particle size distribution	Particulate Matter	Microbiological limit
Microscopic evaluation	Preservative	pH
Water content	Net content	Dose content Uniformity
Leak rate	Weight loss	Pump delivery
Microbiological limit	Extractables & Leachable	Microscopic evaluation
Valve delivery	Dose content Uniformity	Weight loss
Extractables & Leachable	Foreign matter	Droplet size distribution

❖ Specific Stability test required are given below:

Appearance and Color: The appearance of the content of the container and the container and closure system should be appropriate and it should be confirmed to their description.

Assay: The Assay is performed to determine the concentration of drug substance in the container should be determined analytically.

Degradation Products: This test is accessed to determine the level of degradation products and impurities. Acceptance criteria should be set for individual and total degradation products and impurities.

Dose Content Uniformity: This test is performed to determine Discharged dose per actuation. The number of actuations per determination should not exceed the number of actuations in the minimum dose approved in the labeling.

Aerodynamic particle size distribution: This test is performed to determine the particle size distribution of the outgoing aerosol. The optimum aerodynamic particle size distribution has been recognized as being in the range of 1–5 microns.

Microscopic Evaluation: drug substance particle size is determined by performing microscopic evaluation of the formulation.

Leak Rate: This test is performed to maintain optimal performance characteristics for the drug product and it should meet acceptance criteria.

Moisture Content: This test is performed to check the presence of water or moisture in the container or not. As the presence of water will change the drug product characterization so it should be checked.

Microbial Limits: This test is performed to check that the drug product does not support the growth of microorganisms and that microbial quality is maintained throughout the expiration period.

Valve Delivery: This test is performed to check to the metering ability of the valve, and it evaluates valve-to-valve reproducibility of the drug product.

Leachable: The drug product should be assessed for components that leach from plastic components or coatings of the container and closure system.

Sterility: All aqueous-based Inhalation and Nasal drug products must be sterile it should be labeled as sterile and confirmed by testing.

Particulate Matter: This test is used to check the presence of particulate matter in the drug product. Levels of particulate matter in the drug product should be determined. The acceptance criteria should include limits for foreign particulate matter less than 10 micrometers (mm), greater than 10 mm, and greater than 25 mm.

pH: For Inhalation solution, the pH or apparent pH, as appropriate, of the formulation should be tested and an appropriate acceptance criterion established.

Preservatives and Stabilizing Excipients Assay: If preservatives are used in the formulation, there should be a specific assay for these components with related acceptance criteria.

Net Content: Inhalation drug products should include acceptance criteria for net content of the formulation in the container. The net content of each test container should be in accordance with the release specification.

Weight Loss: Inhalation drug products should include acceptance criteria for weight loss on stability. Storage orientation plays a role in assessment of the sealing characteristics of the container closure system, weight loss for the drug product stored in upright and inverted or upright and horizontal positions should be evaluated.

Pump Delivery: This test is assessing to determine pump-to-pump reproducibility in terms of drug product performance.

Spray Content Uniformity: This test should provide an overall performance evaluation of a batch, assessing the formulation, the manufacturing process, and the pump. This test is designed to demonstrate the uniformity of medication per spray consistent with the label claim, discharged from the nasal actuator, of an appropriate number.

❖ LABELING REQUIREMENTS^[5]

The label is Identity of a product. It is beneficial to consumers as well as to let them distinguish product from one another. The significance of label is to provide information to a prospective customer about ingredient of the product. Label also identifies the product through its patented color and design. It also describes the product that made it, contents, how to used, quantity, and also include legal stipulation like MRP, expiry date, contraindication.

LABELING REQUIREMENT OF INHALATION AND NASAL PRODUCT AS PER US^[3]

➤ **Product Title:** To standardize the nomenclature for oral inhalation sprays, the established name of all such drug products should include the designation (Drug Substance) Inhalation Spray, for nasal sprays the drug product would include the name (Drug Substance) Nasal Spray. The established name should be followed by a phrase such as For **Oral Inhalation Only, or For Nasal Use Only as appropriate.**

➤ **Label**

- Established Name of the Drug product
- Amounts of the drug substance delivered from the pump nasal actuator or mouthpiece
- Number of medication sprays per container
- Net content (fill) weight
- Usual dosage
- Excipients (established names)

- Route of Administration
- Recommended storage conditions including any warning statements regarding temperature or light exposure
- Manufacturer's and/or distributor's name and address
- "Rx Only" statement
- Lot number
- Expiration date
- Use period once drug product is removed from protective packaging (if applicable)
- Instructions regarding shaking of suspension drug products
- NDC number (recommended)

➤ **Patient Package Insert**

- A figure that displays the various elements of the container closure system.
- Instructions for initial priming and for re-priming of the unit.
- A statement cautioning against spraying the eyes with the formulation.
- For inhalation spray drug products, a statement instructing the patient to confirm the absence of foreign objects in the mouthpiece before using the product and after removing the protective mouthpiece cap, where applicable.
- Storage conditions should be clearly stated, including any warning statements regarding temperature and light exposure.
- Appropriate cleaning instructions should be included (if applicable)
- If protective packaging was used, appropriate statements should be included that the drug product should not be used after a specified number of days (e.g., 2 weeks, 30 days) from the date the protective packaging was removed

LABELING REQUIREMENTS AS PER EUROPE^[4, 6]

- **Product Title:** It should include Name of Drug product.
- **Label:** It should include following
 - The Brand Name of product;
 - The common Name of Finished Product;
 - The standards of drug it any;
 - The Route of Administration;
 - The Method of Administration;

- The Expiration Date;
 - The Batch number;
 - Content by weight/by volume/by unit;
 - Marketing Authorization holder number;
 - Dosage Strength;
 - Manufacturing Date;
 - Recommended storage conditions;
 - Adequate Direction for use of the product
 - POM (Prescription only Medicine) statement
- **Patient package insert**
- Warning statement should be clearly stated.
 - Information about Active pharmaceutical ingredient and its use.
 - Use in special population
 - Appropriate cleaning instructions should be included.
 - Precaution regarding use of Inhaler should be given.
 - Possible side effects should be included.
 - Instruction for use should be given.
 - Instruction need to know before use of product
 - Storage conditions should be clearly stated
 - Content of formulation and other information that should be included.
 - Information regarding how to use the product that should be given.
- Tertiary package labeling should include following requirements:
- Name of medicinal product
 - Statement of API
 - List of excipient
 - Pharmaceutical form and content
 - Method and route of administration
 - Special warning
 - Expiratory date
 - Special storage condition
 - Special precaution for disposal of unused medicinal product

- Name and address of Marketing Authorization holder
- Marketing Authorization number
- Batch number
- General classification for supply
- Instruction on use

CONCLUSION

Stability testing is key component in the pharmaceutical development. Stability studies of Inhalation and Nasal products are carried out that recommended storage condition and shelf life can be included on the label to ensure that the medicine is safe and effective throughout its shelf life. The regulatory requirements have been made increasingly stringent to achieve above goal in all possible conditions to which the product might be subjected during its shelf life. Stability studies which are required for Inhalation and Nasal product are same for both the countries. The studying the stability guideline we can easily find out the shelf life of the product which is necessary for pharmaceutical companies to file their product in US and Europe. Labeling Requirement is more stringent in US as there are more specific information is given as well as more specific patient related information are also given compared to Europe.

ACKNOWLEDGEMENT

The Authors are thankful to Dr. K. Pundarikakshudu, Director of L. J. Institute of Pharmacy, Ahmedabad, India for providing all the facilities and encouragement to carry out the work.

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