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Pharmaceutical stability testing: An overview of stability

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A regulating body's approval of a proposed drug substance retest period and proposed drug product shelf life depends on the data generated from stability testing. The stability data of pharmaceutical products are crucial because they correlate to the quality, safety, and efficacy of the product. This article, the first of three on pharmaceutical stability testing, provides readers with an overview of stability and its importance in drug safety and highlights the common pitfalls of stability testing programs. The second article addresses stress testing, and the third, bracketing and matrixing designs for stability testing. The series is based on current stability guidelines from the International Council for Harmonisation (ICH).

Keywords – deficiencies, stability, testing

Introduction

The stability of the drug substance and drug product in the pharmaceutical setting correlates to the quality, safety, and efficacy of these highly regulated pharmaceutical products. In this article, we will discuss the specific principles defined in the ICH Q1A(R2) guideline on stability testing protocol and explore how those principles contribute to the reliability of stability testing and the safety of medications.[1]

Stability, as defined in the ICH Q1A(R2) guideline, measures how pharmaceutical products maintain their quality over time under various environmental factors such as temperature, humidity, and light encountered during transportation and storage before consumers can use the product.[1] Stability testing is considered a routine procedure during product development. It establishes the shelf life of the drug product and the recommended storage conditions and defines the retest period for the drug substance.

Stability testing programs are costly and can be time-consuming for manufacturers. However, they generate valuable data that can significantly benefit the manufacturer over time and can support their continuous

production process improvement strategies. The data can benefit the company long-term by providing years worth of data that can support an extended expiry/shelf life showing that the substance or product is stable over a significant period of time.

A full glossary of terms, including *drug substance, drug product, shelf life*, and *retest period*, which are used the preceding text, is at the end of this article.

The importance of stability

The purpose of stability testing is to ensure that the final drug product is safe for patient use and to provide assurance for the end user that the drug product will remain at an acceptable level of quality while it is available on the market. Drug manufacturers must take precautions to offset the environmental factors or variables that can affect product stability.

It is crucial when testing for drug substance stability to also establish the *retest date* (see Glossary) for when the material should be reexamined to ensure its suitability and potency for subsequent use in the drug product has been maintained. If a batch of drug substance is destined for use in the manufacturing of a given drug product, then the result of the retest should remain within established specifications. The ICH Q1A(R2) and ICH Q1E guidelines provide recommendations on how to establish a drug substance retest date.[1,2]

One of the main objectives of drug product stability testing is to determine the product shelf life, which is a compulsory regulatory label component that must be displayed on the outer packaging of the product. The *expiration date* (see Glossary) ensures the quality and potency of the product will remain consistent within the established shelf life, provided the product is stored according to the recommended conditions outlined in ICH Q1A(R2).[1] The shelf life is established based on the stability test data and is vital to obtaining regulatory approval from health agencies.

Another important aspect of stability testing is determining the suitable packaging components for the drug substance or drug product. The ICH Q1A(R2) guideline recommends that stability testing be conducted on the *dosage form* packaged in the proposed commercial *container closure system* (see Glossary) so the data generated can reflect a real-time condition.[1]

Typically, the drug product samples for these stability studies are kept upright rather than inverted or on their sides, which would represent the worst-case This is to allow the product a full interaction with the container and would help determine whether the contact between the drug product and the closure would result in extraction of chemical substances from the closure components or any adsorption of the product into the closure parts. At a minimum, a

suitably selected container should protect the drug product from physical damage, biological contamination, and external influences, such as heat and light, that could alter the properties of the product.

In addition, the container closure system would also be subjected to a range of package stability tests, including checks for the presence of extractables and leachables, container closure integrity, and conditions during shipping distribution. Quality control tests of the pharmaceutical packaging materials will vary depending on the type of packaging selected.

Similarly, any potential incompatibility between the drug substance and all packaging components should be identified. The drug substance's reactivity to the packaging will determine the type of packaging that is needed for storage. Once the reactivity parameters have been identified, they should be routinely tested to ensure their consistency and acceptability for continued use of the packaging during storage.

A range of adverse effects, such as the loss of potency in an active drug substance, can occur if drug substance stability is not achieved and maintained throughout the specified shelf life. For example, aspirin is hydrolyzed in the human body during normal consumption for an indicated condition. However, if the tablets are stored in moist or humid conditions, they could begin hydrolyzing before being used by patients and become less potent and therefore less effective when eventually used as a treatment.

Types of stability

Pharmaceutical stability can be divided into two categories: premarket (developmental) and marketed (commercial). The former aims to generate data to support ongoing clinical trials. The latter ensures stability assurance of postapproval batches for monitoring long-term stability. In either case, stability-indicating tests are performed on drug substances and drug products to establish the retest period and shelf life.

In either stability category stability-indicating tests are performed on the drug substance and drug products to establish the retest period and shelf life. The stability of a drug substance or product can be broadly categorized into five types. The final drug product is deemed safe for use only if the following aspects of stability are fully demonstrated:

- **Chemical stability –** analyzes how the active pharmaceutical ingredient maintains its potency and integrity;
- **Physical stability –** refers to properties such as appearance;
- **Microbiological stability –** analyzes the resistance of microbial growth;
- **Therapeutic stability –** ensures that therapeutic effect is maintained; and
- **Toxicological stability –** assesses any significant increase in toxicity that would harm patients.

Relevant analytical methodologies should be used to determine the complete stability-indicating profile of a drug substance or product, such as the use of high-performance liquid chromatography, ion exchange chromatography, and peptide mapping, among others.

Global stability zones

Different global climate conditions must be taken into consideration when managing storage. In accordance with ICH Q1A(R2) and the World Health Organization's (WHO) stability guideline, there are four stability zones across the world (**Table 1**).[1,3] The same drug product could have different storage conditions depending on the climatic zone in which it will be marketed.

Stability requirements at the initial filing

Under ICH guidance, the amount of stability data required at the time of an original submission (e.g., new drug, marketing authorization, biologics license applications) will depend on the type of product and type of container closure system, intended label storage condition, type of stability studies, and the storage condition. A general overall requirement is presented below in **Table 2** (p. 5).[1,3]

Stability testing on drug substances and drug products

A robust stability protocol should be in place before any stability testing program is started. The protocol should set out the executable plan of the stability program, detailing the design of the program and the information to be recorded. The scope of information outlined in the protocol could include a range of aspects such as details about the product, its packaging, manufacturing process, storage conditions, and testing schedule.

Batch selection

Typically, three primary batches are used for drug substance and drug product stability testing in stability studies. For drug substances, the selected study

Table 1. Global stability zones[1,3]

Zone	Type of climate	Temperature, °C [range, °C]	Relative humidity, % [range, %]
I	Temperate	21 [±2]	45 [±5]
II	Mediterranean/subtropical	25 [±2]	60 [±5]
III	Hot and dry	30 [±2]	35 [±5]
IV	Hot and humid/tropical	30 [±2]	65 [±5]
IVb	Hot/higher humidity	30 [±2]	75 [±5]

Table 2. General stability requirements for initial filing[1,3]

Intended label storage condition	Stability studies	Storage condition		Minimum submission requirements, months
		Temperature, °C [range, °C]	Relative humidity, % [range, %]	
Room temperature	Long term Intermediate Accelerated	25 [±2] or 30 [±2] 30 [±2] 40 [±2]	60 [±5] or 65 [±5] 65 [±5] 75 [±5]	 12 6 6
Refrigerator	Long term Accelerated	5 [±3] 25[±2]	NA 60 [±5]	12 6
Freezer	Long term	-20[±2]	NA	12

NA, not applicable

batches should be on a pilot scale at a minimum and the method used should simulate the process to be used during production of the drug substance batches. (*Pilot scale* refers to a small-scale preliminary study conducted to evaluate the feasibility, cost, and duration. It is also performed to identify possible improvements to process design/methodology before the development of a full-scale study.) In addition, the container closure components used in the stability test should be the same as those proposed for storage and distribution.[1]

Stability testing for drug products should be carried out in batches of the same formulation and packaging intended for commercialization, meeting the same commercial specification intended for marketing. If the container closure components in stability studies are not the same as the intended final packaging components for either the drug substance or drug product, then comparability studies of the different container closure components should be conducted to ensure that the differences will not affect the stability profile of the drug substance and drug product.

Setting specifications

Drug substance and drug product stability testing should include attributes that are susceptible to change over time during storage and those that are likely to affect quality, safety, and/or efficacy. Typically, this testing should cover physical, chemical, microbiological, therapeutic, and toxicological attributes and should use fully validated and stability-indicating analytical procedures.

Testing frequency

The requirements for testing frequency depend on the type of study and storage conditions. For long-term studies for which the proposed retest period

of a drug substance is at least 12 months, testing is required every three months for the first year, every six months for the second, and annually for each subsequent year through the proposed retest period. A similar testing frequency applies to a drug product with a shelf life of at least 12 months.

For *accelerated storage conditions* in a six-month study, testing is required a minimum of three times over the study period: once at the start of the study and then at three and six months. For *intermediate storage conditions* in a 12-month study, a minimum of four *time points* is required: once at the start of the study, and then at 6, 9, and 12 months (see Glossary).

In addition, from a regulatory planning perspective, a reduced stability database can be submitted to support application for the approval of a new dosage of a drug product that contains the same active ingredients as an existing approved drug product. In such a scenario, six months of accelerated and six months of long-term data from ongoing studies are typically required for submission.[4]

Storage conditions

Both the drug substance and drug product should be subjected to storage conditions that would test thermal stability and sensitivity to moisture. A minimum of 12 months for long-term testing should be carried out on three primary registration batches at the time of submission and should be continued to include the proposed retest or shelf-life period. There may be certain scenarios in which it is possible to submit less than 12 months of long-term stability on the primary registration batches but only with prior agreement with the agency. Primary registration batches are defined as drug product batches manufactured and used for the registration and approval of the drug product.

Evaluation of stability data and extrapolation

ICH Q1E focuses on the evaluation of stability data.[2] The evaluation of stability data is important because it helps determine the appropriate storage conditions for pharmaceutical products to ensure their stability and potency. Stability evaluation assists in establishing shelf-life specifications and providing patients and healthcare professionals with accurate information about the product's expiration date. It also helps pharmaceutical manufacturers make informed decisions about product labeling, storage, and distribution.

Extrapolation is a way of extending what is known about something to make predictions about what is not known. It involves using existing data or patterns to estimate how a system will behave in the future or in situations in which data are limited. This method assumes that the observed behavior will prevail even outside of the known range.

In stability studies, there may be a need to determine how a material or system will behave over an extended period. However, running stability tests for the

entire expected duration may not always be feasible because of time, cost, or practical constraints. This is where extrapolation can be used. While extrapolation is a valuable tool, it is important to recognize its limitations. Extrapolating too far into the future or outside the range of available data can introduce uncertainties and inaccuracies. Factors such as environmental conditions and/or the presence of unknown variables can affect the accuracy of extrapolations. Therefore, it is crucial to exercise caution and validate extrapolations with additional data whenever possible. For example, consider a new drug product that has been developed and that needs to be evaluated for stability. The manufacturer needs to estimate its shelf life, but there are only six months of stability data available. By analyzing the available data, the company can extrapolate the drug's stability over a longer duration by assuming the degradation rate of the drug observed in the initial six months will remain relatively constant.

Failure in stability testing

In an ideal setting, complete stability test results are within the specified acceptance criteria. However, in reality, there may be times when stability batches will not meet the specification(s). During a stability study program, the approved stability protocol must be followed for all selected batches. If any batch shows out-of-specification (OOS) results for any test parameter at any time during the study, the specific test parameter may be retested to rule out analyst error, depending on company policy. If the parameter fails on retest, then the stability study for this batch will typically continue to the next time point. This batch will continue to be monitored for the duration of the stability protocol for any stability trends to determine whether they will have any impact on the quality of the drug product batch.[1]

If, after the point at which the OOS result occurred and the remaining time-point results are still acceptable, then the batch is still considered stable, provided the OOS results have been fully justified to ensure there is no impact on the stability study. However, if all time-point results are within specification but fail at the last time point, a justification must be provided to support why the batch is still acceptable. If other batches in the program show the same issue, that is, failure at the last time point, it could result in a reduced expiration date or retest date.[1]

If the stability batches have any OOS or unexpected trends, it is good practice to provide a justification to ensure that these batches are stable and that the OOS or unexpected trends have no impact on the quality of the drug substance or product.[1]

Common stability deficiencies

Stability batches that fail to meet specifications are cause for concern. Equally, all requirements of the stability study must be fulfilled to ensure a successful stability study program. Some of the common stability pitfalls are lack of:[5]

- A valid sample size and test intervals based on statistical criteria for each attribute examined;
- Appropriate storage conditions for samples retained for testing;
- Reliable, meaningful, and specific test methods;
- Testing of the drug product in the same container closure system that is intended for commercialization; and
- Testing of drug products for reconstitution at the time of dispensing as well as after reconstitution.

It is important to note that an adequate number of drug product batches must be tested to determine an appropriate expiration date.

Conclusion

As increasingly complex pharmaceutical products are being developed and manufactured, regulations will also be adapted to ensure that the quality, safety, and efficacy of these regulated products remain adequate. From the regulatory agencies' perspective, the stability aspect will always be taken into detailed consideration during the review process. Therefore, manufacturers should aim to fulfill all the stability requirements to ensure a successful and fully justified stability program.

Abbreviations

ICH, International Council for Harmonisation; **OOS,** out of specification; **WHO,** World Health Organization.

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References

All references accessed and/or verified on 16 April 2024.

1. International Council for Harmonisation. Stability testing of new drug substances and products Q1A(R2). Dated 6 February 2003. Accessed 21 April 2023. https://database.ich.org/sites/default/files/Q1A%28R2%29%20Guideline.pdf
2. International Council for Harmonisation. Evaluation for stability data Q1E. Dated 6 February 2003. Accessed 21 April 2023. https://database.ich.org/sites/default/files/Q1E%20Guideline.pdf
3. World Health Organization. Annex 10. Stability testing of active pharmaceutical ingredients and finished pharmaceutical products. 2018. Accessed 25 April 2023. https://database.ich.org/sites/default/files/Q1F_Stability_Guideline_WHO_2018.pdf
4. International Council for Harmonisation. Stability testing for new dosage forms – Annex to the ICH harmonised tripartite guideline on stability testing for new drugs and products Q1C. Dated 6 November 1996. Accessed 21 April 2023 https://database.ich.org/sites/default/files/Q1C%20Guideline.pdf
5. Therapeutic Goods Administration [Australia]. Common deficiencies in stability data and trial design. Updated 6 March 2017. Accessed 21 April 2023. https://www.tga.gov.au/resources/resource/guidance/stability-testing-prescription-medicines/145-common-deficiencies-stability-data-and-trial-design

Glossary[1]

Accelerated storage condition. The condition under which a drug substance or drug product is stored at elevated stress conditions – such as temperature, humidity, and pH – to provide data for predicting the degradation rate or physical changes. (Temperature and relative humidity in the accelerated storage condition would be 40°C and 75%, respectively, versus 25°C and 69% for suitable long-term storage conditions.) In the accelerated storage condition, testing is recommended at a minimum of three time points, including the initial and final time points (e.g., at zero, three, and six months in a six-month study).

Container closure system. A container closure system comprises the primary and secondary packaging components that contain and protect the dosage form. The primary packaging container closure system is made up of the packaging components that contain and protect the dosage form. The secondary packaging refers to the exterior packaging that groups the primary packages, provides additional information about the dosage form, and carries the identifying branding for the dosage form.

Drug substance. An active, unformulated ingredient with a specific pharmacological activity. The drug stance can be formulated with inactive ingredients to produce the dosage form.

Dosage form. The physical form in which a drug is administered (e.g., tablet, capsule, lozenge, powder, ointment, solution, eye drops, lotion, inhaler-administered medications).

Drug product. A finished dosage form (e.g., tablet or solution) that contains an active drug ingredient and usually, but not always, inactive ingredients.

Expiration date. The drug expiration date marks the date before which the product is known to remain stable, that is, it retains its strength, quality, and purity when it is stored according to its labeled storage conditions.

Intermediate storage condition. Intermediate conditions are generally 30°C/65% relative humidity to moderately increase rate of chemical degradation or physical changes in the drug substance or drug product (suitable long-term storage, 25°C/69% relative humidity). Testing is recommended in the intermediate storage condition if there is significant change in the

accelerated storage condition. The testing frequency should be at a minimum of four time points, including the initial and final time points (e.g., 0, 6, 9, and 12 months), from a 12-month study.

Pilot scale. A pilot scale study is a small-scale preliminary study conducted to evaluate the feasibility, cost, and duration. It is also performed to identify possible improvements to process design/methodology before the development of a full-scale study.

Retest period. The period during which a drug substance or product can be considered suitable for use, provided it meets specific quality criteria. It is determined based on stability data obtained from formal stability studies. A batch of drug substance must be retested after this period to ensure it still meets the criteria, and, if it does, it should be used immediately.

Retest date. The date after which a drug substance should be re-examined to ensure it remains suitable for use. It is determined based on stability data generated during formal stability studies. The retest date for a drug product is related to its quality control testing. It indicates when the product should be retested to ensure it still meets the required specifications.

Shelf life. The shelf life of a pharmaceutical product is the period for which the product maintains its identity and quality when stored at the conditions defined on the label of the product.

Time point. The designated test date for a drug substance or product in a stability study.