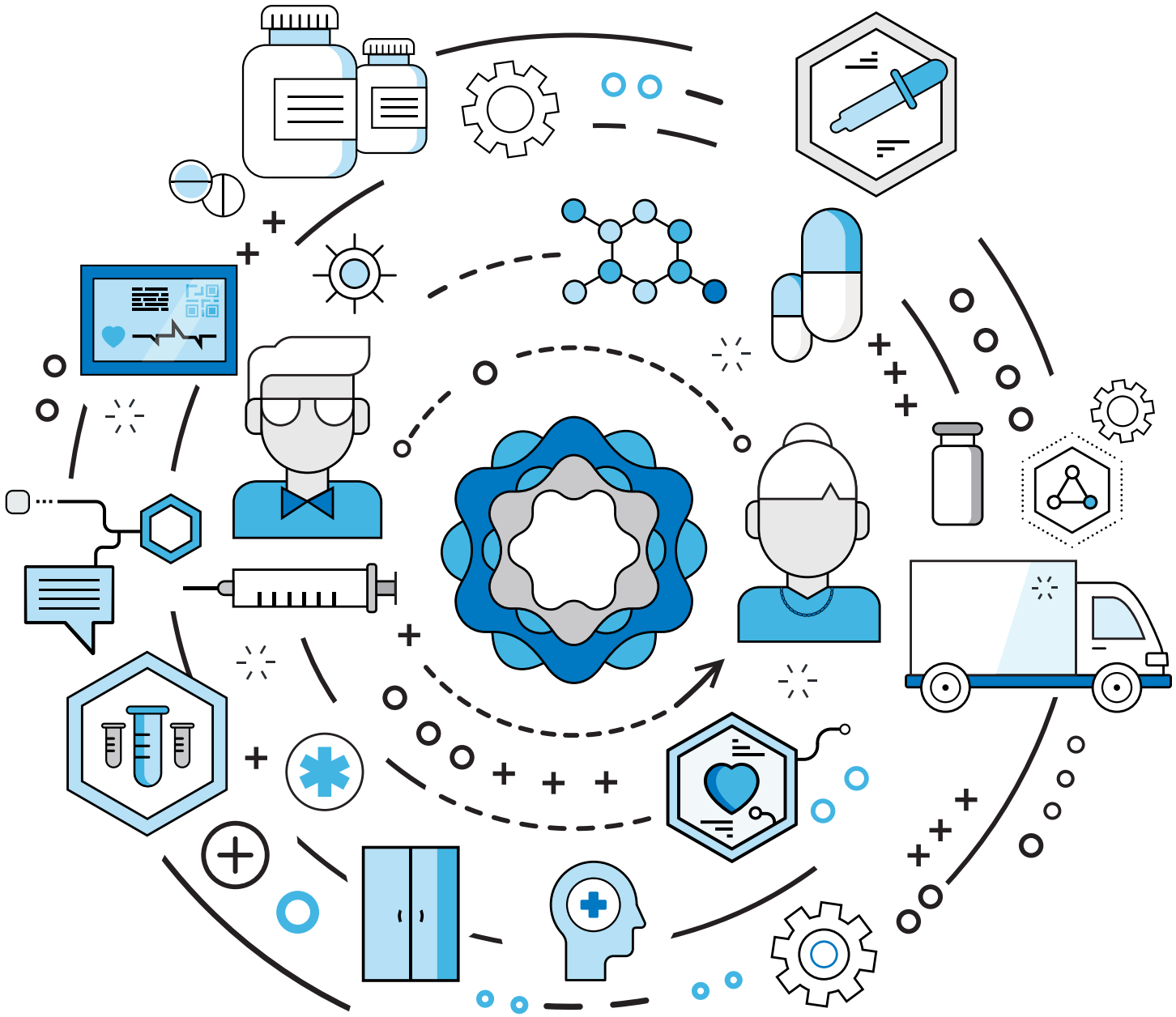

Stability Guide.

Alcami scientific experts go back to the basics to examine the importance of stability in pharmaceuticals.

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Contents.

About the Authors.

Richard "Adam" Keisker, Laboratory Support Supervisor for Alcami's St. Louis site, manages the daily activity of the Laboratory Support Technicians— ensuring laboratory work spaces are equipped and analysts fully prepared to complete their analytical testing. Adam graduated from Lindenwood University with a Bachelor of Arts in Chemistry and is currently pursuing his MBA degree from Western Governors' University.

Russell Crothers, Supervisor of Alcami's St. Louis Sample Control Unit, is a leading authority at Alcami for the generation, review, and edits of stability protocols. Russell is responsible for the execution and management of the commercial and clinical development products for stability and maintains compliance with both ongoing and new regulatory requirements. Under his leadership, Alcami has been able to streamline and digitize processes resulting in more efficient, precise stability services as well as sample control. Russell obtained his Bachelor of Arts in Biology from Greenville University.

Chapter One: The Importance of Stability in the Evaluation of Quality Attributes of Pharmaceutical Drug Products

Exactly how important is stability testing in the life of the active pharmaceutical ingredient (API) or drug product?

The quality attributes that everyone strives for are safety, product efficacy and integrity, appropriate storage conditions, and shelf life. The US Pharmacopeia (USP) defines "stability" as the extent to which a product retains, within specific limits, and throughout its period of storage and use (i.e., its shelf-life), the same properties and characteristics that it possessed at the time of its manufacture <USP1191>. The purpose of stability is to examine how the critical quality attributes of a drug substance vary with time under different environmental factors.

Environmental studies include factors such as temperature, humidity, and light in order to establish a retest period (i.e. shelf life) for the drug substance along with the recommended storage conditions. This process ensures that no physical, chemical, or microbiological changes affect the quality and integrity of the final products.

Storage conditions and shelf life in API and drug products directly take into account the intended markets based on the climate conditions. Four climatic zones have been distinguished for stability testing worldwide: Zone I - IV <ICH Q1A-Q1F>, derived from the mean kinetic temperature of any part of the world.

Climatic Zone		Temperatures	Humidity
Zone I	Temperate	21°C (± 2 °C)	45% RH (± 5%)
Zone II	Subtropical, with possible high humidity	25°C (± 2 °C)	60% RH (± 5%)
Zone III	Hot/Dry	30° C (± 2 °C)	35% RH (± 5%)
Zone IV	Hot/Humid	30° C (± 2 °C)	65% RH (± 5%)
Zone IVb	Hot/Humid*	40° C (± 2 °C)	75% RH (± 5%)
Refrigerated		5° C (± 3 °C)	None
Frozen		-15° C (± 5 °C)	None

These climatic zones are simulated in chambers that involve temperature, humidity, and light under the guidance of International Conference on Harmonisation (ICH) and US Food and Drug Administration (FDA) guidelines.

Through stability testing pharmaceutical companies can help ensure that the product has the most suitable packaging or container closure for storage and distribution. Safeguarding the quality of APIs and drug products.

Chapter Two: The Impact of Stability on the Safety of APIs and Drug Products

Can you answer any of these questions?

- Exactly how safe are your drugs?
- Do you know the active ingredients in the pills that you are taking?
- What is the purpose of your medication?

Let's be honest– most people take these answers for granted. One quality attribute that all companies in the pharmaceutical fields strive for is the safety of drug products. The "Guidance for Industry" put in place by the FDA for drug stability guidelines states: "A drug product is considered unstable when the drug substance (active ingredient) loses sufficient potency to adversely affect the safety or efficacy of the drug or falls outside labeled specifications as shown by stability-indicating methods."
In order to help ensure safety for all consumers, pharmaceutical drugs undergo different trials/phases including, but not limited to, the following chart.

Molecule Discovery	Identification, toxicity, and validation of base compounds
Preclinical	Optimization of the molecule in the structure-activity relationship (SAR)
Phase I - III	Chemical development into APIs and undergoes process and research development and safety
Formulation Development	Stability, solubility, and bioavailability of product
Manufacturing	Validation, raw materials, and quality control of product

Contract development and manufacturing organizations (CDMOs) prioritize safety through each individual step from a stability standpoint during method development, formulation development and manufacturing of the raw material.

How does stability help with the safety of pharmaceutical drugs?

Stability is one of the MOST important steps in an evaluation of drug safety and efficacy. Going back to the basics with quality attributes, stability plays a tremendous role in product development. When a product is placed in the International Conference on Harmonisation (ICH) conditions and evaluated through a spectrum of testing (physical, chemical, biological and microbiological) at different time intervals, we are able to monitor degradation of the active pharmaceutical ingredient (API)/finished product. Degradation can develop at any point of these trials. In fact, even the smallest amount of degradation could cause adverse effects on consumers.

Stability's purpose is to show how changes in light, temperature, pH, humidity or just overall time can affect the API/finished product. Therefore, this trending of shelf life is essential in maintaining drug effectiveness, thus directly related to the product safety and toxicology of the product.

Not only is stability essential in the testing of pharmaceutical drugs, the 21 CFR 211.94 of the current good manufacturing practices (cGMP) regulations ensures that the drug product container and all closures meet all of the requirements to ensure safety. Knowing how the packaging and storage container affects the product over time are additional variables that are taken into account to protect the safety of the consumer.

Ultimately, the number one priority of any regulatory committee, and the number one priority at Alcami, is consumer safety.

Chapter Three: Measuring Shelf Life– Product Efficacy of API and Finished Drug Products

The FDA states that “Stability studies should include testing of those attributes of the active substance that are susceptible to change during storage and are likely to influence quality, safety, and/or efficacy. The justification of individual and total upper limits for degradation products should be based on safety and/or efficacy consideration.”

Safety, quality, and product efficacy work together in stability studies of APIs and finished drug products. Pharmaceutical companies, like Alcami, have the ability to identify and trend shelf life and their affects on efficacy as samples are exposed to time, light, and temperature

In order to learn why stability studies are so important in establishing efficacy, one must first understand the terms defined in this chart.

Efficacy[1]	Maximum effect that a drug can produce regardless of does or amount of a drug that is needed to produce a given effect
Effectiveness[2]	Measures the accuracy or success of a diagnostic or therapeutic technique when carried out in an average clinical environment (real world setting)
Potency[1]	Amount of drug needed to produce a given effect (also known as strength— usually expressed in dosage, such as milligrams)
Degradation[3]	Condition or process of degrading or being degraded (decline to a lower quality, condition, or level)
Shelf Life[4]	Time at which the average drug characteristic remains within an approved specification after manufacture (decay to 90% of its original concentration)
Expiry Date[5]	Time in which a drug product in specific packaging configuration will remain stable when stored under recommended conditions

The FDA regulates API and finished drug product efficacy, and both must demonstrate effectiveness to gain approval. In finished products, stability storage and testing are taken into consideration. Stability storage and testing demonstrate how products withstand degradation when exposed to varying temperatures, humidity, and light.

All finished products approved by the FDA have established levels of efficacy, and potency can significantly impact side effects. For instance, a drug may have very good efficacy but is so unpleasant to take, due to side effects and amount of degradation, that its actual effectiveness within the margin of safety is extremely limited. With stability storage and testing, we are able to identify these potential issues.

In stability studies, the inherent stability characteristics of the molecule, particularly the degradation pathways, must be identified. Degradation correlates with the effectiveness and the efficacy of the finished product in order to measure the shelf life of a product. Scientists are able to identify the degradation in the product form and the suitability of analytical procedures for the quantification of both the active substance and degradation products to establish retest periods. Thus, stability studies are ultimately determining the shelf life of the finished product.

A shelf life determines a timeline for when a product is considered safe and effective under relevant storage conditions. Such factors as temperature and relative humidity can be used to accelerate these processes effectively allowing for trending and prediction of shelf life.

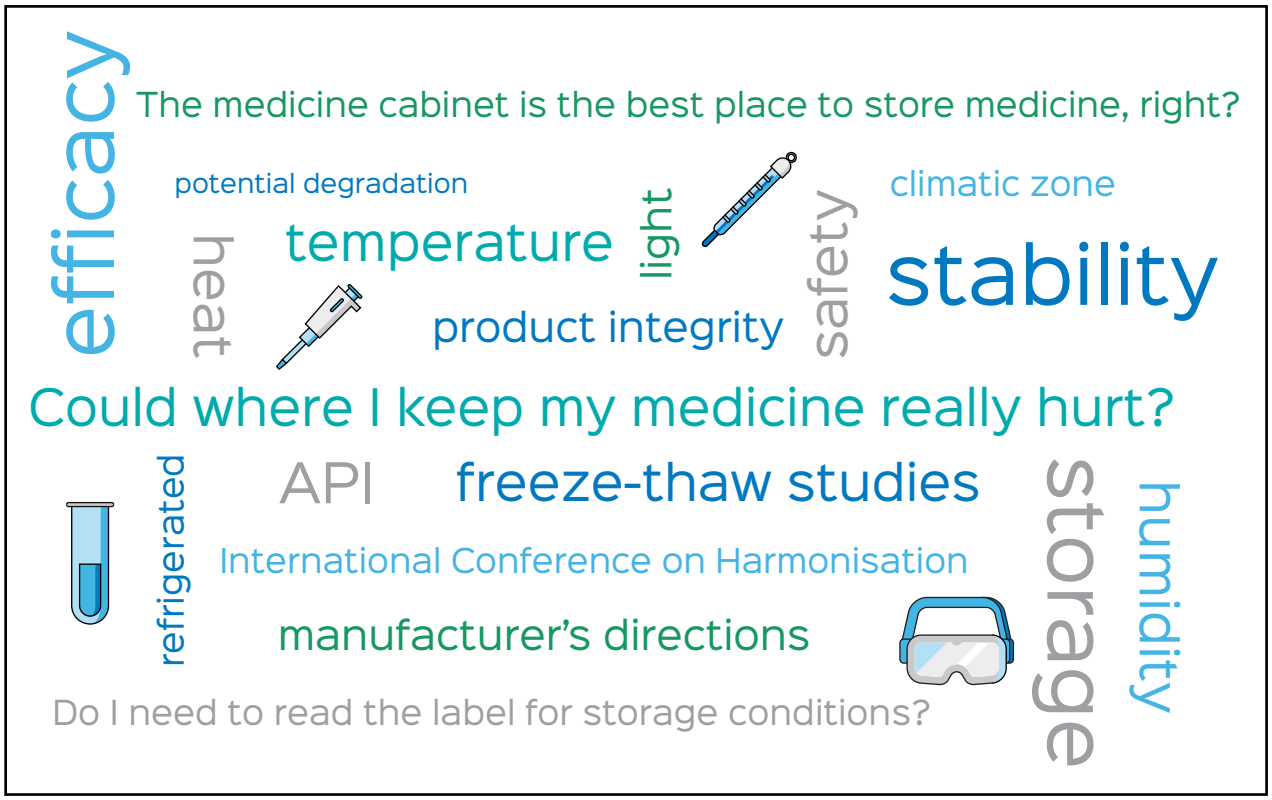
Fundamental degradation factors involving the efficacy and shelf life of APIs/ finished drug products are listed in the chart below.

Physical	Changes to the physical nature of the drug (appearance, properties, hardness, brittleness, particle size) occurring in tablets, capsules, semisolids
Chemical	Separation of the chemical compound into elements or simpler compounds or change in the chemical nature (hydrolysis, oxidation, isomerization, polymerization, photodegradation)
Microbiological	Contamination of a product (depending on the type of microbe and its level of toxicity)

Provisions regarding the particular formulation are in place to ensure maximum efficacy and safety of the product, as well as the container, to remain within particular chemical, microbiological, and physical specifications as guided by ICH. Alcami offers stand-alone stability services as well as in-process studies with the expertise to guide you from the design of the stability study for each phase of development through the evaluation of the data accruing to ICH Q1E.

Chapter Four: Stability and the Importance of Storage Conditions

This fourth chapter of the Stability Guide will answer the most common questions people have about storing medicines and explain how storage plays a direct role on a product's efficacy, along with which studies are used to measure efficacy.



Is it necessary to read the storage conditions listed on the label?

Could where I keep my medicine damage it?

Yes! How medicine is stored influences its efficacy and safety. Remember to always follow the recommended storage conditions for the best use of a finished pharmaceutical product.

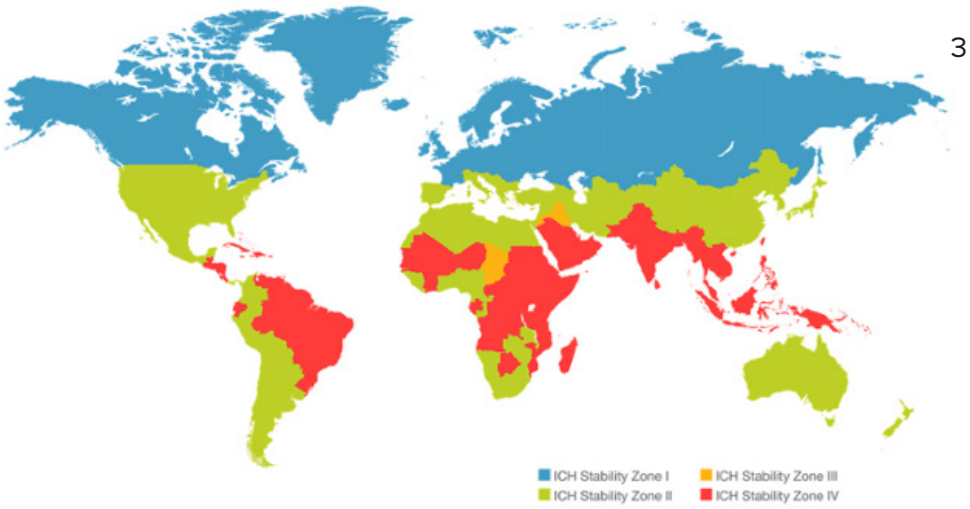
Heat, humidity, and light are all responsible for degradation of products. Regulation committees, such as the FDA, ensure that proper precautions are taken in order to maintain consumer safety. Establishing product integrity within different climate zones is essential because just the slightest change in temperature and humidity could affect medicines.

Stability storage and testing studies are performed to simulate climatic effects.

The studies are based on where the products are going to be sold. Knowing all the ways a finished product or APIs could be affected by degradation is crucial in the storage of these products.

From those studies, Alcami is able to establish a shelf life of the medicine, determine the best way to store the medicine, and ultimately help ensure the safety of the consumer.

ICH distinguishes four worldwide climate zones as listed in the map below.



[3]

- Zone I: temperate
- Zone II: subtropical, with possible high humidity
- Zone III: hot/dry
- Zone IV: hot/humid

Accelerated studies, or forced degradation, are used to predict the shelf life of a product. Scientists speed up the processes and rate of decomposition/degradation by increasing the temperature and/or humidity of environmental conditions for a brief period of time. These accelerations demonstrate the impact to the medicine if introduced to extreme conditions for a short period of time. Overall, this gives a general overview of the different properties of degradation including physical, chemical, and microbiological.

Freeze-thaw studies determine whether the formula will remain stable under various conditions. Freezing is a common processing step used to maintain stability and quality of a drug substance during development and production of the medicine. The finished product/APIs are put through a series of rapid changes that could be encountered during shipping and handling of samples. The sample goes through a cycle of freezing conditions, usually around negative 20°C, and placed in higher temperature conditions, typically 25°C – 45°C, then tested. This cycle will occur over a span of a couple of days/weeks. The testing looks for any significant differences of the overall product throughout the entirety of the study.

Listed below are the ICH guidelines for the different study parameters and the minimum time requirements needed to support the data. Please note that relative humidity is referred to as RH.

General case - room temperature

Study	Storage Conditions	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

* SADC GUIDELINE FOR STABILITY TESTING - March, 2004

Refrigerator

Study	Storage Conditions	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

* SADC GUIDELINE FOR STABILITY TESTING - March, 2004

Freezer

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

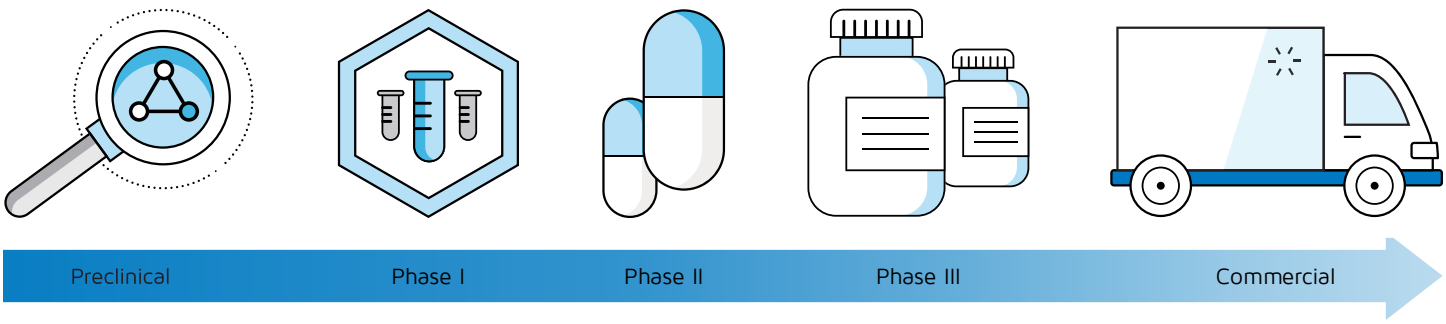
* SADC GUIDELINE FOR STABILITY TESTING - March, 2004

These parameters are set in place so pharmaceutical companies can establish strong data to support optimal storage conditions based on climate zones. Simulating these conditions and seeing how, over time, the product efficacy is affected is the purpose of stability.

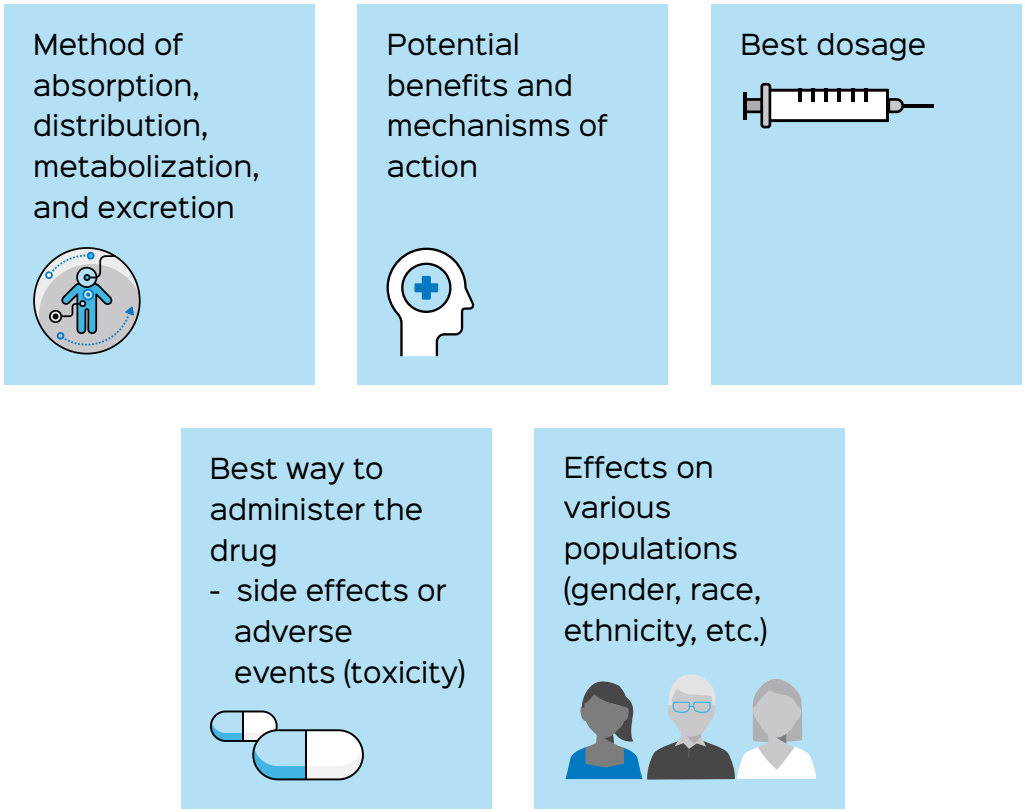
In closing, remember to always properly store medicine in accordance with the manufacturer's directions. Alcami is an industry leader in stability expertise and capabilities offering full ICH storage conditions, redundant facility capacity, and any unique studies required like in use, photostability, and freeze/thaw.

Chapter Five: The Summation of Stability and Quality Attributes

The final post in this series examines the summation of stability's role in the drug formulation process. From molecule discovery through product release to market, quality attributes are carefully analyzed to support product success and protect patients.



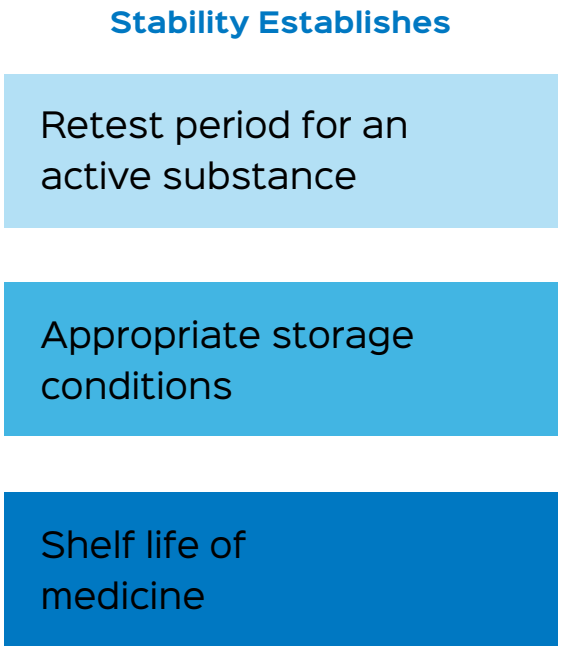
In the first step of the drug formulation process, drug discovery or the non-clinical phase, researchers investigate new understandings about a disease and design a product to stop or reverse its effects. Advanced technologies are explored, often to either target drug substances/active pharmaceutical ingredients (APIs) to specific locations within the body or to manipulate genetic material. During this phase, extensive research and development on how the finished product will be formulated also occurs.



After this information is collected, the preclinical phase monitors the efficacy of the product and its potential to cause harm. These studies provide detailed information about the dosing and toxicity of the drug substance. Based on these findings coupled with meticulous research, a decision can be made whether or not to proceed to the clinical research phase.

Stability becomes a major factor in Phase III, where it undergoes validation. Companies manufacturing finished goods or APIs conduct stability testing based on guidances outlined in the ICH. ICH focuses on the quality, safety, efficacy, and multidisciplinary structures of a product. As guided by the ICH, data should be provided on a minimum of three primary batches of drug product or API to establish product shelf life and suitable storage conditions. It is important to follow ICH guidelines when selecting batches, showing that "the overall quality of the batches of API placed on formal stability studies should be representative of the quality of the material to be made on a production scale."

Once the batch selection is completed, a retest period would be applicable to all future batches manufactured under similar circumstances. This retest period determines whether the degree of variability from testing of the individual batches will affect the future production of a batch. If the product remains within certain specifications throughout the assigned retest period, the manufacturer can replicate the data of consistent batches.



The finished product goes through this guided testing to pinpoint particular degradation pathways. The ICH Q1A (R2) Stability Testing of a New Drug Substance and Products states: “The nature of any degradation relationship will determine whether the data should be transformed for linear regression analysis. Usually, the relationship can be represented by a linear, quadratic, or cubic function for an arithmetic or logarithmic scale.” Patient safety and ICH compliance are at the forefront of the development of the medicine during the stability process.

We, at Alcami, pledge to prioritize stability studies with every drug formulation, testing, and manufacturing procedure we conduct to help ensure we are working in a safe, connected way with our clients and their patients.

In conclusion, stability is an integral part of the drug development process. With every stability study, it is essential to focus on the quality attributes of the product– most importantly safety. Throughout this blog series, Alcami scientists discussed stability testing procedures, the "how" and "what" of degradation in the measurement of shelf life, the importance of storage conditions, and the necessity of following a medication's recommended guidelines.

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Chapter Four

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*Delivery time is dependent on product formulation and process needs

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