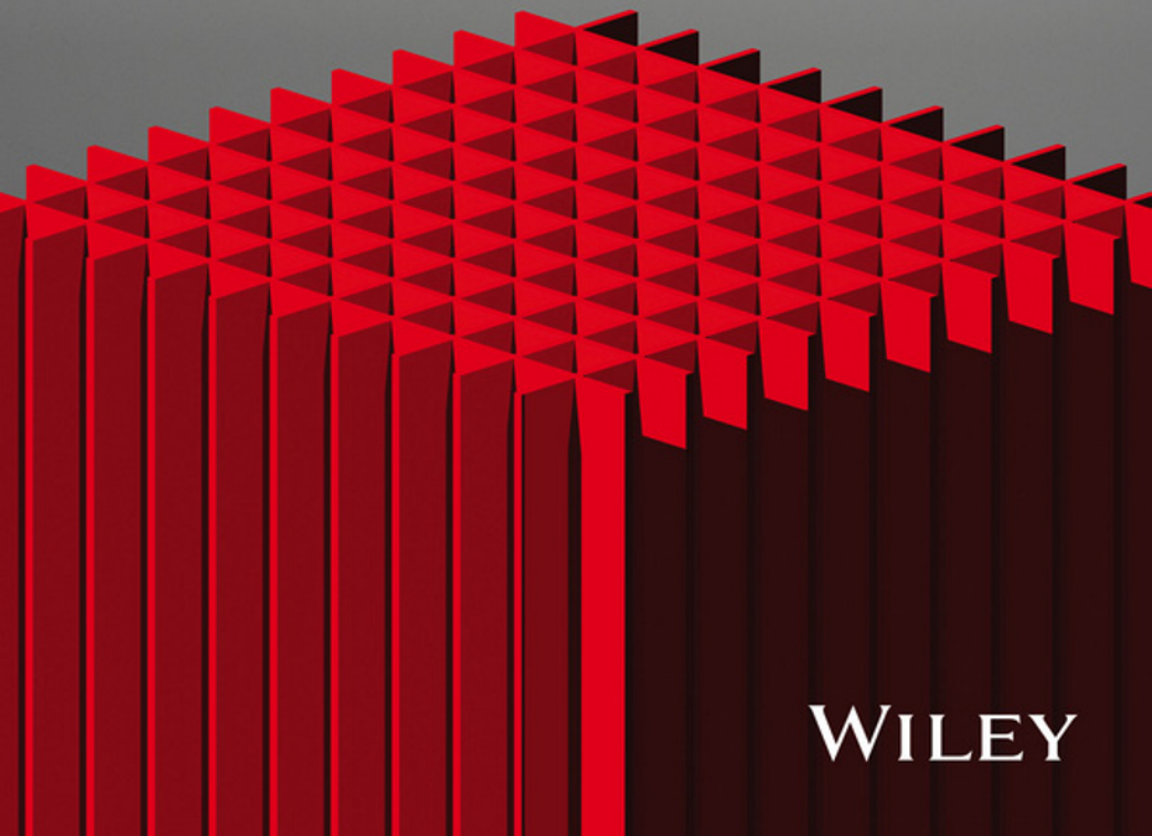
ICH Quality Guidelines

An Implementation Guide

Edited by Andrew Teasdale, David Elder, Raymond W. Nims



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An Introduction to ICH Quality Guidelines

Opportunities and Challenges

The International Conference on Harmonisation (ICH) of technical requirements for registration of pharmaceuticals for human use was initiated in April 1990. ICH had the initial objective of coordinating the regulatory activities of the European, Japanese, and the United States bodies (along with the pharmaceutical trade associations from these three regions), to discuss and agree the scientific and technical aspects arising from product registration. This was recently supplemented by the addition of Health Canada and Swissmedic, to the core ICH Steering Committee (SC) [1].

At the initial ICH SC meeting the terms of reference were agreed and it was decided that harmonisation initiatives would be divided into Safety (S), Quality (Q), and Efficacy (E), reflecting the main criteria which underpin the approval and authorization of new medicinal products. It was subsequently realised that several topics were multi-disciplinary (M) in nature.

Thus, ICH's mission was to realize greater harmonization in both the interpretation and application of requirements for new product registration, with the objective of minimizing repetition/duplication of both testing and reporting, which is routinely performed as part of the development of new medicinal products. Harmonizing these differences via the ICH guidelines would help industry reduce development times, save resources and benefit the patient.

It is difficult not to underestimate the benefits of the ICH initiative in general and the ICH Quality guidelines in particular (and those related Multi-Disciplinary guidelines), to the CMC community. Although it is fair to state that not all of the guidelines have been equally successful; it is very clear that the majority have been very successful and there is an ongoing recognition of the need to update and maintain the guidance in line with new developments and technological advances. Furthermore, the desire to extend the benefits of harmonisation beyond the ICH regions through collaborative efforts is to be welcomed and brings us a step closer to global harmonisation of these important principles of medicinal product evaluation. As part of the objective to extend its global outreach, ICH recently welcomed new regulatory members

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from Brazil and South Korea. In addition regulatory authorities from Cuba, Kazakhstan, and South Africa were also agreed as ICH Observers [2].

The success of the ICH guidelines, in many ways has been due to the adoption of overarching principles and a guidance framework describing the main requirements for compliance without being overly prescriptive. Yet while varying levels of detailed information has been included in the different guidelines to facilitate understanding, it has left many seeking further clarification on the practical application of the guidance. The purpose and benefit of this book is that it allows the reader a deeper insight provided through dedicated chapters into the practical aspects of a specific guideline's application.

Each of the chapters seeks to examine the key requirements of the specific guidelines and then considers the challenges both in interpretation and practical implementation. It is this perspective, looking behind the basic framework; and then examining both the intent and practical guidance that I believe will make this text an essential aid to those involved in CMC matters, both from an industry and regulators' perspective.

To achieve the intended goal the Editors have pulled together an unrivalled collation of subject matter experts aligned to each chapter, many involved directly in the derivation of the ICH guidelines themselves.

Dr David Tainsh, Chief Product Quality Officer, GSK

References

1 SwissMedic. ICH Meeting in Minneapolis, USA: SwissMedic and Health Canada Included as New Members, July 9, 2014. https://www.swissmedic.ch/aktuell/00673/02270/index.html?lang=en. Accessed on February 27, 2017.

2 ICH. Press Release Osaka Meeting, November 17, 2016. http://www.ich.org/ichnews/press-releases/view/article/ich-assembly-osaka-japan-november-2016.html. Accessed on April 12, 2017.

1

ICHQ1A(R2) Stability Testing of New Drug Substance and Product and ICHQ1C Stability Testing of New Dosage Forms

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1.1 Introduction

A core part of the medicines development process is an understanding of the chemical and physical behavior of the active ingredient and the medicinal product into which it is incorporated under the storage and usage conditions they are likely to encounter. The International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH) stability guidance provides a foundation and framework for this endeavor.

Stability testing was one of the first quality, safety, and efficacy topics harmonized across the ICH territories (Europe, USA, Japan, Canada, and Switzerland) in tripartite guidance. The latest revision of ICHQ1A Stability Testing of New Drug Substances and Products was adopted in 2003 [1]. It forms the parent guideline to a suite of associated guidelines providing more details on recommended stability practice. The guideline provides information on storage conditions and duration and testing requirements that should be used to generate the core stability data package in support of product registration in the ICH regions. To encompass the behavior of different drug delivery platforms and their input drug substances, the guideline contains some flexibility in the requirements. Importantly, the guideline also includes an introductory statement recognizing that alternative stability approaches can be used if scientifically justified. A short annex to the parent stability guideline is embodied in ICHQ1C, which addresses the stability requirements for a new dosage form when an applicant develops a new product variant following an original drug substance and drug product application [2].

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As worldwide registration is the goal for many medicinal products, the standardization and simplification of the global supply chain for a new medicine, via harmonized stability and labeling practice, is desirable. While the intent of the guideline is to recommend the data sets required to register new drug substance and products in the three main ICH regions, its content is cited and used much more widely. The ICH guidelines are also referenced in territorial guidance beyond the ICH regions either on a stand-alone basis or in support of local stability guidance. For example, the World Health Organization (WHO) is a long-standing observer of the ICH process, leading to the incorporation of much of the content of the ICH into its own stability guidance [3].

The ICH stability guidance not only is intended for registration purposes but also informs stability practice during development, for example, the storage conditions described in the guidance can provide a framework for the development stability protocols used to underwrite the quality, safety, and efficacy of drug product used in clinical studies.

While the guidance embodies a traditional approach to stability protocols, the principles described in terms of the stability performance requirements for pharmaceutical products have also been translated into targets for predictive stability screening tools. These tools can provide assurance that when formal stability studies to support product registration are performed in accordance with ICH guidance, the likelihood of obtaining unexpected results is reduced.

Some stability testing requirements are linked with specific product platforms and are detailed in other guidance. Examples include instructions relating to studies that justify in-use storage, strategies to demonstrate the suitability of protective secondary packaging, and specific studies to underwrite temperature excursions during storage and transportation.

In the "quality by design" era, where pharmaceutical development practice is guided by science- and risk-based approaches, highlighted in three more recent ICH guidelines on pharmaceutical development [4], risk management [5], and pharmaceutical quality system [6], the focus for stability studies has evolved further to emphasize the importance of generating detailed stability knowledge and understanding. This may include establishing the attributes of the input materials (drug substance and excipient) and any processing parameters that are critical to stability performance. Following identification of the attributes critical to stability, an integrated control strategy should be established to ensure the attributes remain within acceptable limits, thereby assuring that the required stability performance is demonstrated. The use of risk management tools to ensure development activities are focused on the areas that will have the most influence on the control of stability (and therefore quality safety and efficacy) is also a feature.

From a practical perspective, the goal of performing stability testing on products intended for global registration remains challenging, requiring the development of a protocol that will result in a high probability of approval in all

major markets. Regions with their own specific stability requirements can make the development of a truly "global" registration protocol more challenging. For example, the guidance on stability study requirements for the registration of drug products in countries forming the ASEAN region of Southeast Asia recommends a different long-term storage condition compared with the ICH regions [7].

This chapter aims to provide an understanding of the fundamental principles behind stability testing and then demonstrate how the guidance is typically applied during pharmaceutical development.

1.2 The Fundamental Science That Underpins Stability Testing

1.2.1 The Stability Process

Quality, safety, and efficacy must be maintained throughout the shelf life of a medicine, from manufacture to the end of shelf life and when being used by the patient. This can be achieved by developing an understanding of the chemical and physical properties of the product so that it is possible to establish methods to control and monitor the critical parameters and establish the long-term behavior of the drug substance and medicine.

The regulations require an expiry date on drug products or a retest date on active pharmaceutical ingredient [8]. For drug product, the expiry date defines the period within which the drug product is expected to comply with its approved control specification limits when stored under the recommended conditions. Similarly, a retest date is assigned to drug substance. If a drug substance batch is required for drug product manufacture beyond its labeled retest date, it should be retested to confirm continued compliance with specification prior to use. Stability testing provides the means to investigate how a medicine behaves under different environmental conditions and demonstrate that a pharmaceutical product maintains its fitness for use throughout this labeled shelf life. The stability testing of drug products involves evaluating them on storage over time in the container/closure system intended for use in the clinic or the commercial market.

The stability of a pharmaceutical product is the result of a complex interplay between environmental factors (temperature, humidity, availability of oxygen, and exposure to light), and the intrinsic chemical and physical stability of active ingredients and formulation excipients. The conditions under which these ingredients are processed to form the medicine, and the degree of protection provided by any primary and secondary packaging are also influencing factors.

The stability process involves finding out what degradation pathways are available to a new chemical entity, what steps can be taken to assess the extent

of degradation most likely to be encountered under normal storage, and what strategies are available to prevent or limit any observed degradation. Chemical breakdown constitutes a major factor in drug or formulation failure on storage, but physical, biological, and microbiological changes can also be a source of instability.

Chemistry driven changes include changes in product quality or product performance characteristics caused by

- Increase in levels of degradation products with potential impact on safety
- Potency loss associated with chemical breakdown/reaction of active ingredient with potential impact on efficacy
- Change in visual, taste, or odor caused by increased levels of degradation, with potential impact on overall product acceptability

The extent of chemical breakdown does not need to be significant for potential problems to occur, for example, formation of low levels of a breakdown product that gives rise to specific safety concerns or small amounts of a highly colored degradation product affecting visual appearance.

1.2.2 Factors Affecting Stability

Demonstrating stability knowledge and appropriate control involves developing an understanding of the factors that can affect the stability of a medicine and confirming that appropriate controls are in place to assure quality, safety, and efficacy throughout the labeled shelf life. These factors include

- The intrinsic stability of the active pharmaceutical ingredient(s)
- Input excipient properties and how they affect the stability of the API
- The unit operations associated with the manufacturing process
- Environmental factors (external, internal, and microenvironment)
- The materials and functionality associated with any packaging system

Further factors affecting product stability are outlined in Figure 1.1

1.2.2.1 Intrinsic Stability of the Active Pharmaceutical Ingredient

Pharmaceuticals are often developed as salts of organic acids or bases in order to achieve the desired physicochemical properties. Ironically often the functionality that imparts the desired efficacy in a medicine may also make the molecule less stable. Pharmaceuticals are generally composed of carbon skeletons with additional functional groups. Electron distribution, bond polarity, and steric factors associated with the carbon skeleton can all affect stability. Factors affecting the electron distribution or electron density, in a drug molecule, can greatly affect its susceptibility to degradation. For example, double bonds alternated across a structure can impart stabilizing conjugation via delocalized electron density. The conjugation can make a molecule more rigid

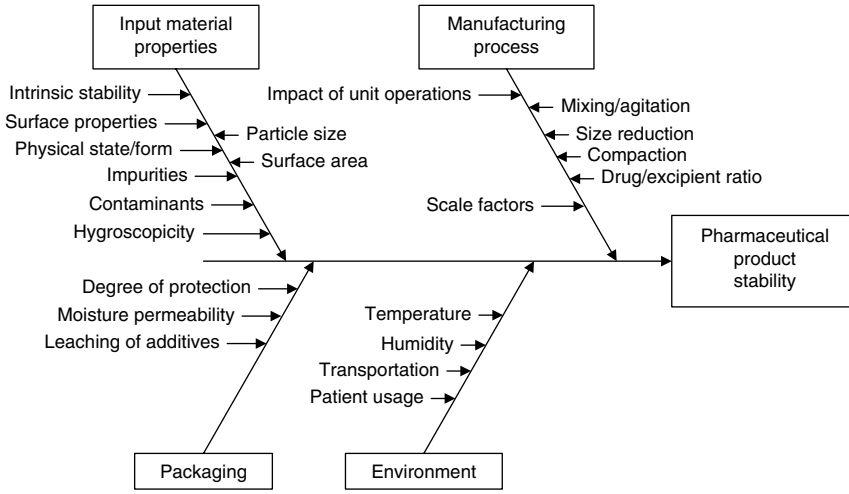


Figure 1.1 Factors potentially affecting product stability.

and also enhance the absorption of UV light. The delocalized electrons can act as a conduit for the transmission of electron density or full negative or positive charge, and this resonance can stabilize charged species making them more likely to form. Inductive effects can result in bond polarization, a movement of electron density across the bond depending on the electronegative or electropositive nature of substituents. Substituent groups can profoundly affect the reactivity, and therefore stability, of pharmaceuticals. Neighboring substituents may interrupt conjugation inhibiting electron delocalization and the potential for resonance stabilization. More often neighboring substituents, especially the bulky ones, prevent a reagent getting to the reaction site, particularly true for nucleophilic substitution (S_N2) reactions. Similarly, the presence of a bulky counterion such as chloride can protect the salt-forming center of the drug substance from oxidative attack. These are all examples of steric hindrance.

Knowledge of the shape and molecular arrangement in tandem with the knowledge of how functional groups react enables theoretical prediction on how a new chemical entity might behave under given physical and chemical conditions [9].

Knowledge of the environment within the formulation allows prediction of those conditions that may initiate or catalyze the reactions causing breakdown.

Therefore, developmental stability programs should be designed to demonstrate how robust a product is to environmental conditions of heat, humidity, and light. These programs are often more extreme than the default ICH storage conditions as there is a desire to accelerate the degradation to

allow meaningful decisions to be made in shorter time periods. Screening studies to investigate chemical reactions with extraneous species such as process impurities or formulation or packaging additives should also be considered as well as studies to assess the potential for physical changes to occur on storage.

1.2.2.1.1 Degradation Reaction Pathways

Chemical Breakdown There are four main reaction mechanisms, all of which may occur as part of a degradative process: substitution, addition, elimination, and rearrangement. Degradation reactions can be broadly categorized as hydrolysis, oxidation, photolysis, and isomerization or rearrangement. In addition, specific interactions between the active molecule and functional groups on excipients, process-related impurities, or extraneous contaminants may also result in additional degradation reaction pathways.

Hydrolysis Due to the ubiquity of water as a potential reactant, the most prevalent reaction mechanism associated with degradation reactions is hydrolysis. Derivatives of carboxylic acids such as esters, amides, imides, lactones, lactams, and acid chlorides are particularly susceptible [10]. It is difficult to completely eliminate water from solid drug products, and it is also the most commonly used solvent for parenteral products. The general reaction for carboxylic acid derivatives is shown:

$$\mathrm{RCOOR' + H_2O \rightarrow RCOOH + R'OH}$$

Water acts as a nucleophile attacking electron-deficient or electropositive sites within drug molecules. The acyl derivatives ester, amide, and imide are most prone to attack, and acid or base can catalyze the reaction.

Alkaline hydrolysis involves the initial nucleophilic attack of a hydroxide ion on the electropositive center and then, for example, in the case of an ester, elimination of the alkoxy substituent to form an acid and alcohol.

In acid-catalyzed hydrolysis of esters, the carbonyl oxygen is protonated and then water nucleophilically attacks the electron-deficient carbon center. Aromatic esters are more reactive compared with aliphatic.

The products are the same via either mechanism. Heat/light and local pH can also catalyze hydrolysis.

Although this is a second-order reaction, if water is present in a large excess, it will exhibit pseudo-first-order kinetics.

A similar situation occurs with solvents that can act as nucleophiles and this is termed solvolysis. The polarity (or dipole moment) of the solvent is an important factor in such reactions.

Protecting an active ingredient that is prone to hydrolytic degradation naturally involves limiting the presence of unbound water, which would be available for reaction. Using a suitable moisture barrier with low water permeability in

the primary and/or secondary pack will reduce the amount of moisture being transported from the external environment inside the pack. Employing a desiccant such as silica gel, using excipients with low moisture content or excipients that can adsorb unbound water such as colloidal silicon dioxide, will also help to maintain low humidity levels inside the protective pack. As extremes of pH can cause hydrolytic breakdown, the use of buffers (more often in solution dosage forms but there are solid state buffer systems in use as well) can stabilize a system.

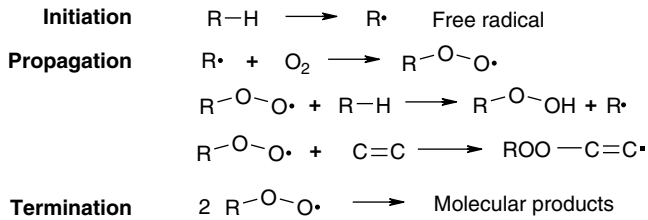
Oxidation Due to its presence in the atmosphere, oxygen represents another readily available reactant for potential degradation mechanisms. Where the reaction occurs with aerial oxygen, this is often called "autoxidation." The oxidation mechanism also includes the addition of an electronegative atom, such as oxygen, or a radical or the loss of an electropositive atom, such as hydrogen, a radical or an electron [11]. Aldehydes, amines, ethers, phenols, thiols, thioethers, and unsaturated fat/oil functionalities are particularly prone to oxidation. The mechanism and resulting degradation product profile can be complex, and it is often associated with discoloration.

General reaction: $R-R+O_2 \rightarrow R-OO$

Oxidation is probably the second most common degradation mechanism.

Oxidation of pharmaceuticals often occurs by direct reaction with atmospheric oxygen under ambient conditions. Usually this is a free radical reaction resulting initially in the formation of hydroperoxides that may react further. This is called auto-oxidation.

The free radical mechanisms can be complex involving initiation, propagation, and termination steps, and many auto-oxidation reactions can be catalyzed by trace amounts of metal ions or hydroperoxides present as impurities. For example:



A free radical is a highly reactive atom or molecule with an unpaired electron. Formation of a free radical, in an initiation step leading to further reaction, can be catalyzed by the presence of trace metal and/or trace peroxide or exposure to light, heat, or base.

Propagation involves formation of a peroxy radical, which can then abstract protons to form a hydroperoxide or add to a double bond to form an addition

product radical. Hydroperoxides can decompose in the presence of free radical initiators to form peroxy and alkoxy radicals. The alkoxy radical can abstract protons to form alcohols or react with oxygen to form the corresponding acid, aldehyde, or ketone, which may react further. Termination involves two radicals combining to form stable molecules.

Inhibiting the oxidation of labile active ingredients involves preventing exposure to oxygen and light through use of a suitable barrier; sparging solution formulations with inert gas (such as nitrogen, carbon dioxide, helium) is also employed in specific cases. The inclusion of an antioxidant system such as a chelating agent to remove any free metal ions and labeling with a lower storage temperature may help. Addition of an antioxidant system, to preferentially remove oxygen or scavenge for any free radicals, may also stabilize a formulation that is prone to oxidation. If an antioxidant system is added to aid stability performance, an assay for antioxidant content is usually performed to monitor its continued effectiveness. Where the use of excipients that are prone to auto-oxidation is required, the selection of grades that contain minimal levels of aldehyde or peroxide contaminants will help to limit oxidative degradation.

Photolysis Photolysis involves degradation initiated or catalyzed by electromagnetic radiation (artificial or natural light). In a photolytic degradation mechanism, energy absorbed by the molecule is sufficient to activate degradation [12]. Oxidation, reduction, isomerization, rearrangement, decarboxylation, dealkylation, dehalogenation, and dehydrogenation pathways can all occur. Aromatic and conjugated heterocyclic molecules, aldehydes, and ketones are all susceptible. Complex mixtures of degradation products may result.

One description of photodecomposition is light-induced free radical-initiated breakdown, which is not mediated by molecular oxygen. Normal sunlight or artificial light can initiate photolytic degradation. If the electronic spectrum of a molecule overlaps with the spectrum of sunlight or artificial light, energy can be absorbed, and the molecule reaches a higher or excited state (electron promotion to a higher orbital, making the molecule more reactive). The excited state either dissipates the energy—excited electrons returning to their original orbital or reaction occurs by molecular decomposition or energy transfer with other molecules. Saturated molecules containing single bonds do not react in this way, but molecules containing double bonds can absorb light, so consequently aromatic carbons and their heterocyclic analogs, aldehydes, and ketones are the most susceptible. Substituted 1,4-dihydropyridine antihypertensive agents, for example, nifedipine, demonstrate this behavior, where different substituents can influence their photostability [13]. Many potential mechanisms exist often resulting in complex mixtures of degradation products.

Prevention of photolytic breakdown involves reducing the light transmitted to the active ingredient. The use of suitable protective barrier layers (opaque

plastic, low actinic amber-colored glass, aluminum), with reduced or no light transmittance, can provide some degree of protection for products susceptible to photodecomposition. In addition, colorants such as titanium dioxide or hydrated alumina lakes used in tablet film coatings and capsule shells may also behave as opacifiers, providing light protection for the underlying formulation. As seen previously with oxidation, scavenging molecules can minimize free radicals and hence inhibit the photolysis reaction and the use of low impurity excipients and chelating agents to remove any potentially catalytic metals all potentially prolong the shelf life of photolabile active ingredients. Protection can also be achieved by employing complexes such as cyclodextrins or use of surfactants to form a protective micelle. Excipients that preferentially absorb light may also be included in the formulation, such as titanium dioxide.

Isomerization A pharmaceutical molecule may be a geometric or stereo isomer. Isomerization is used to describe the process of conversion of a single stereoisomer into its conformational, optical, or geometric isomers [14]. The functionality and steric effects associated with the parent molecule are important. Any unwanted isomer may have different or potentially undesirable activity or be inactive. The unwanted isomer is usually treated an impurity/degradation product (see ICH Q6A).

Stereoisomers possess the same molecular formula and bonding arrangement but different orientations of the same groups in space. They can be geometric isomers or enantiomers. Isomerization usually occurs via a mechanism that involves an intermediate carbon, which is positively or negatively charged and resonance stabilized.

1.2.2.2 Reactive Species and Their Potential Origin

Formulating an active drug substance usually involves dissolving in a suitable solvent, dispersing in a suitable vehicle, or intimately mixing with excipients. Each additional ingredient may contain potential reactants, present as impurities, which might cause degradation. For example, polysaccharide excipients containing free aldehyde or ketone moieties (termed reducing sugars) can undergo an addition/elimination reaction with amine groups (Maillard reaction [15]). Further degradation mechanisms can therefore be available where the active ingredient interacts with the functional groups on the formulation excipients or with any extraneous contaminants or impurities present in the excipients (e.g., residual metals, aldehydes, or epoxides [16, 17]). In addition, more than one active pharmaceutical ingredient may be combined in the same formulation.

Excipients may not react themselves, but if they are hygroscopic, this may pull water into a formulation containing a moisture-sensitive drug. Similarly, a hydrated excipient might lose its water of hydration on mechanical processing,

Table 1.1 Origin of extraneous contaminants that may influence stability.

Potential reactive species or catalyst	Potential source
Water	Fairly ubiquitous, bound, or unbound
Acidic species	Poly(oxy)ethylenes including PEGs
Alkaline species	Dicalcium phosphate, some stearates
Metal ions	Manufacturing plant, talc, and other silicates, poly(oxy)ethylenes
Leachable materials (e.g., phthalates or volatile organic hydrocarbons)	Manufacturing plant, transfer lines, seals, containers, and closures
Antioxidants	Oils/lipids, magnesium stearate, plastic, and rubber contact materials
Peroxides	Povidones, tweens, poly(oxy)ethylenes
Aldehydes	Starch (formaldehyde), lactose, and poly(oxy)ethylenes

and this water may act as a reagent or transport medium facilitating other reactions, particularly if the drug substance is manufactured in its amorphous form or contains localized amorphous regions [18]. Table 1.1 shows some potential degradation reactants or reaction initiators and their pharmaceutical origins. Trace metals or peroxides could act as catalysts in the formation of free radicals. Extremes of pH can potentially leach potential reactants out of the surfaces associated with manufacturing equipment such as trace metals from high grade stainless steel or silicates from glass.

The potential for excipients to be a source of reactive species emphasizes the need to characterize their impurity profile extensively and to conduct compatibility studies to select suitable excipient combinations.

1.2.2.3 Environmental Factors

One of the key external factors that can affect stability is the prevailing temperature and humidity conditions associated with the intended marketing territories. On the basis of their prevailing yearly climate and mean kinetic temperature, the world can be divided, broadly, into four sectors or *climatic zones*; see Table 1.2 [19, 20]. The ICH tripartite regions are represented by climatic zone II. Representative long-term storage conditions for each zone have been derived and can be used in stability protocols to underwrite a shelf life in the specific region. A single long-term storage condition (30°C ± 2°C/65% RH) for climatic zones III and IV was originally recommended in ICH Q1F. Following further discussion some countries required specific long-term storage conditions, leading to the withdrawal of ICH Q1F. The recommended long-term storage requirements for regions represented by climatic zones III and IV are now defined in the WHO stability testing guidelines [3].

Table 1.2 Climatic zones.

Climatic zone	Description	Derived long-term storage condition
Zone I	Temperate	21°C ± 2°C/45% RH ± 5% RH
Zone II	Subtropical and mediterranean	25°C ± 2°C/60% RH ± 5% RH
Zone III	Hot and dry	30°C ± 2°C/35% RH ± 5% RH
Zone IVa	Hot and humid	30°C ± 2°C/65% RH ± 5% RH
Zone IVb		30°C ± 2°C/75% RH ± 5% RH

The local external environment such as the factory, the warehouse, and the hospital and community pharmacy shelf all will usually have some degree of associated temperature control and/or monitoring. Road or air freight transport conditions can present a concern if they result in an uncontrolled environment with respect to temperature, pressure, and vibration. Transportation conditions can be controlled to some degree but at increased cost. The concept of good distribution practice (GDP) has been introduced to cover the warehousing and wholesale distribution of pharmaceuticals including guidance on quality systems and storage/transportation practice [21, 22]. The domestic environment is usually perceived as a much less controlled environment, and the medicine should be designed to withstand the environmental conditions and physical stresses typically encountered during normal storage and use by the intended patient population.

Another aspect of the active ingredient, usually considered as part of the preclinical screening process, is the stability of potential new chemical entities under local physiological conditions during administration, for example, the low pH of the stomach for oral administration and high humidity conditions in the nasal cavity or inside the lungs.

1.2.2.4 The Environment Inside the Primary Pack

As primary packaging materials can affect the environment to which the medicine or active pharmaceutical ingredient is exposed, the influence of the primary pack on stability performance must be clearly understood [23]. The primary product packaging and the moisture content of the formulation constituents predominantly influence the prevailing equilibrium conditions inside the product pack. The product pack is important as it determines how much water vapor or any other volatile species can be transferred to/from the external environment. Any moisture ingress into the pack becomes available for sorption by the formulation. Hygroscopic formulation constituents can increase the driving force for moisture transport into the pack. As packaged medicines will tend to reach equilibrium with their external surroundings, the permeability of the packaging component materials will influence the time taken to reach this equilibrium. For example, the use of low permeability

induction seals can prolong equilibration time for solid drug products with screw-topped caps/snap on lids. Plastic blisters have some degree of associated permeability, slowing down the time to reach equilibrium further. The permeability can be expressed as a moisture vapor transmission rate (MVTR). If the MVTR for the packaging material is known, it can be combined with the humidity-adjusted Arrhenius equation (the parameters of which are determined using an iso-conversion approach in an accelerated stability assessment program or ASAP) to predict the stability of the product as a function of pack and storage condition. The presence of desiccant can also be modeled in terms of moisture take-up and saturation point [24]. See Chapter 4 relating to ICH Q1E for further examination of these factors.

Sealed aluminum foil blisters not only prevent moisture transfer but can also trap any moisture present in the environment during sealing. As the most protective packaging materials are more expensive and therefore add to the overall unit cost of the product, manufacturers need to strike an acceptable balance between the protection and cost elements of the pack. The use of desiccant can maintain a lower relative humidity by preferentially absorbing any moisture present. This equilibrium is usually reached fairly rapidly in relation to the overall shelf life. The amount of desiccant required for a specific pack size can be calculated using a simple calculation [25].

For this reason the guideline requires the assessment of stability in the actual container closure system proposed for long-term storage and distribution or as a minimum a pack that simulates its' characteristics.

1.2.2.5 The Formulation Microenvironment

Pharmaceutical products are mixtures of active ingredient and excipients. They can be considered on a particle level in terms of the formulation *microenvironment*. The local conditions in the region near to the particles of active drug substance can influence stability behavior. For example, the presence of localized moisture may dissolve any drug substance or soluble excipient present and therefore increase molecular mobility and potential for degradation reactions. Solubilization may also alter local pH and therefore reactivity [26].

In the solid state, factors such as crystal lattice defects, the presence of specific impurities or contaminants, or localized amorphous regions, may result in localized high energy "hotspots" where active ingredient molecules are more mobile and therefore more likely to react [27]. The external environment, in terms of temperature and the potential for transfer of moisture, may also affect the formulation microenvironment. Ideally a comprehensive understanding of the microenvironment factors that can affect overall stability performance should be developed.

With an enhanced level of understanding, potential changes to raw materials or process parameters can be risk assessed against their impact on the formulation microenvironment. For example, the effect the relative humidity

associated with the pack and formulation microenvironment has on solid-state degradation reaction rate is relatively well understood. This interdependency is explored further in Chapter 4.

1.2.2.6 Chemical Degradation Reaction Energetics

For a drug to degrade there needs to be a pathway or mechanism resulting in the transformation of the active to the degradant, favorable thermodynamics (a driving force for the change to occur), and favorable kinetics for the reaction to reach equilibrium in time to have a substantive and ultimately negative effect on product quality.

1.2.2.6.1 Degradation Reaction Thermodynamics

For the simplified reaction, drug → degradation product:

$$k_{\text{Rate constant}} = \frac{\text{Concentration of degradation product}}{\text{Concentration of parent drug}}$$

As the most stable state is the one of minimum energy but maximum entropy or disorder, thermodynamics predicts that a degradation reaction will not occur unless the free energy change ΔG is negative. The Gibbs free energy can be calculated as follows:

$$\Delta G = \Delta H - T\Delta S$$

where T is the temperature (K), the enthalpy change ΔH represents the difference in bond energies between reactants and products, and entropy ΔS refers to the degree of disorder.

Enthalpy effects can dominate, but entropy effects can be more significant if breakdown results in a greater number of molecular fragments or a constrained ring system opens during a degradation reaction.

The Gibbs free energy is related to the reaction rate constant via the equation

$$-\Delta G = RT \ln K_{\text{Rate constant}}$$

where R is the ideal gas constant (8.314 J/K/mol) and T is the temperature (K).

1.2.2.6.2 Catalysis

A negative value in free energy does not necessarily mean a reaction will occur. Transition state theory postulates that reactions pass through an activated complex or transition state with a higher free energy, which is then subsequently converted to the products. A catalyst can lower the activation energy, making it easier to pass through the transition state to the degradation product (Figure 1.2).

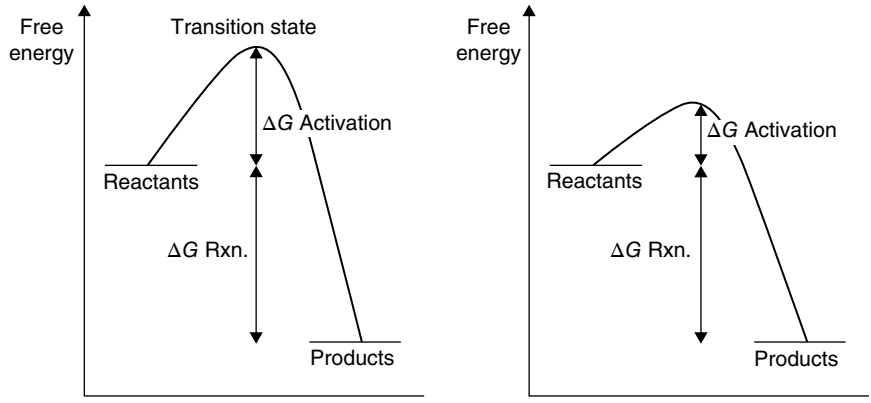


Figure 1.2 Free energy diagram for a degradation reaction.

Electron delocalization may stabilize the resonance of the transition state, facilitating its formation and increasing the likelihood of degradation. This occurs in the light-induced aromatization of 1,4-dihydropyridine-based pharmaceuticals such as nifedipine to form pyridine-related photolytic degradation products. As seen earlier, pharmaceutical excipients, manufacturing equipment, and container closure surfaces may all be sources of trace metals that could catalyze a degradation reaction. Specific drug substances, for example, mycophenolic acid, may chelate trace metal contaminants that can facilitate degradation or result in loss of potency.

Thermodynamics predicts the concentrations of degradant and reactant on reaching equilibrium (if a suitable reaction pathway exists between them) but does not predict how quickly the reaction will reach this equilibrium.

1.2.2.6.3 Degradation Reaction Kinetics

Consider the simple reaction: drug ⇄ degradation products.

If the rate of change of concentration for the drug can be measured, a rate equation can be constructed for the reaction where the rate constant k for a particular temperature and the way the concentration $[D]$ varies depends on a, the overall order of reaction:

$$-\frac{\mathrm{d}[D]}{\mathrm{dt}} = k[D]^{\mathrm{a}}$$

Reaction order can be determined experimentally by making suitable plots of concentration versus time, at a constant temperature, and from these plots the rate constant can also be calculated.

Rate models can be worked out by setting up the differential equation for change in concentration and solving the resulting integral.

For a zero-order reaction, rate is independent of concentration and a plot of concentration against time will reveal the zero-order rate constant.

Likewise for a first-order reaction, rate decreases with time as drug concentration decreases. From the concentration/time profile, we can plot the natural log of concentration against time to yield the first-order rate constant.

Substituting 0.9 for D/D0 allows us to predict the time for which 90% of the active remains (denoted as t_{90}) or 10% degradation has occurred. As this level of change would be the maximum acceptable, t_{90} can be used as an indicator of the potential shelf life that might be expected.

For a second-order reaction, the rate is proportional to the square of the drug concentration where the drug reacts with itself or with a stoichiometric amount of a reactant R. If R is in excess, for example, hydrolysis in aqueous solution, water is in great excess, and therefore the concentration does not appear to change hence the reaction effectively obeys first-order kinetics and said to be pseudo-first order.

In general, zero-order kinetics can be assumed for typical quantitative critical quality attributes such as assay and degradation product levels. This simple assumption forms the basis for statistical assessment of stability data [28].

1.2.2.7 Linking Reaction Rate to Storage Temperature

If degradation data is modeled using appropriate kinetic models and a good fit is achieved, the order of reaction can be obtained, along with a value for the rate constant. This allows prediction of the extent of degradation at a specific temperature.

Within certain constraints the Arrhenius equation can be used to calculate activation energy and predict a rate at different temperatures. The Arrhenius equation predicts the relationship between reaction rate and temperature and forms the basis for accelerated stability testing and shelf life extrapolation:

$$k = Ae^{-E_a/RT}$$

where k is the reaction rate constant, A is the Arrhenius constant, E_a is the activation energy for the specific degradation reaction, R is the general gas constant, and T is the absolute temperature (K).

The equation can be presented in a number of different forms, for example,

$$\ln k = \ln A - \frac{E_a}{RT} \text{ or } \ln \frac{k_1}{k_2} = -\frac{E_a}{R}\left(\frac{1}{T_1} - \frac{1}{T_2}\right)$$

This illustrates how knowledge of a degradation rate at one temperature is used to predict a rate at a different temperature if the activation energy is known (or can be estimated) and a simple linear relationship is assumed.

The relationship between reaction rate and temperature can be visualized using the Arrhenius plot (Figure 1.3).

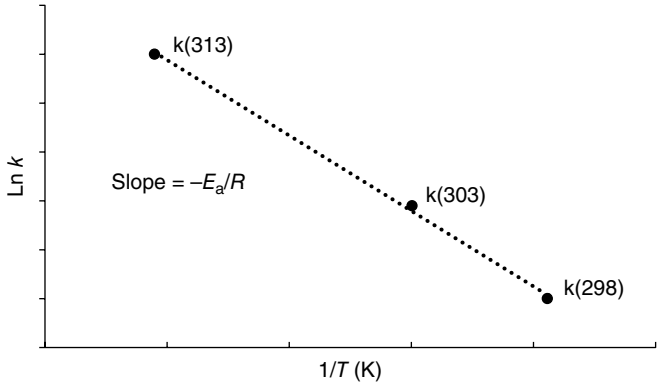


Figure 1.3 Components of the Arrhenius plot.

A linear Arrhenius plot assumes constant activation energy and the same degradation mechanism across the temperatures of interest. Changes such as solubility increase, melting, solvent losses, and formation of volatile degradation products will complicate the model and potentially result in a nonlinear Arrhenius plot. More recently a modified version of the Arrhenius equation has been developed that can be applied to pharmaceuticals to take some of these factors into account and produce much more accurate predictions (see Chapter 4).

Examples of activation energies for typical degradation processes are 85–120 kJ/mol for oxidative breakdown and 60–80 kJ/mol for hydrolytic breakdown [29].

In the absence of definitive activation energy data, assumptions can be made about activation energy, and this can be used as a means of estimating a room-temperature shelf life from higher temperature data. This is often carried out in the early phases of development, when long-term room-temperature data is not available, by extrapolating a predicted shelf life at room temperature from higher temperature data and supporting this extrapolation with subsequent real-time storage stability data.

The simplest of these methods is to apply a "rule of thumb," for example, that a 10°C change in temperature will cause a two- or threefold change in the degradation reaction rate. For example, if supporting forced degradation work indicates the active ingredient is relatively stable and no measurable changes are observed when the product is stored at 50°C for 3 months, a 12- or 18-month shelf life at 25°C could be predicted.

Another approach for general shelf life prediction purposes is to use a lower assay limit or upper limit for degradation as a shelf life target and use available reaction rate data and different estimates of activation energy to make shelf life predictions. This activity can be illustrated graphically or in tabular format.

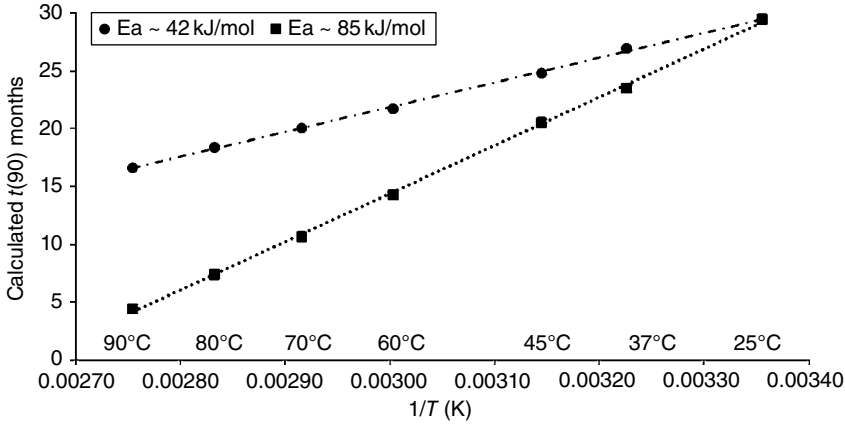


Figure 1.4 Calculation of t_{90} for a specific degradation reaction, using a high and low estimate for activation energy (E_a).

The basis for this method of extrapolation can be illustrated graphically by plotting the predicted time for the product to degrade to 90% of its initial value (t_{90}), against the reciprocal of the storage temperature in Kelvin by using an estimated value for the activation energy for the degradation reaction into the Arrhenius equation.

For example, Figure 1.4 (adapted from reference [30]) develops a shelf life prediction based on obtaining a t_{90} of 3 months for 50°C storage. Using a low value for activation energy for a particular degradation reaction, for example, 42 kJ/mol, a 3-month storage at 50°C is equivalent to about 11-month storage at 25°C. Choosing a higher value for activation energy 85 kJ/mol (a bigger activation energy "barrier" to overcome for the reaction to occur), a 3-month storage at 50°C predicts a shelf life of about 39 months at 25°C.

Another method of applying the Arrhenius equation is to calculate data in tabular format. Using the same assumptions for a lower and upper limit for activation energy, a "stress" or "kinetic equivalence" table can be constructed. For example, the potential stress temperatures and associated duration of the stress test required to predict the shelf life available if refrigerated storage is used can be calculated; see Table 1.3 [31].

These examples demonstrate the different ways the Arrhenius equation supports the prediction of long-term shelf life from short-term data generated at higher temperatures.

The concept of "stress equivalence" derived from the Arrhenius equation underpins the stability protocols and storage conditions described in the stability guideline where higher (accelerated) temperatures are emphasized early in the protocol, while lower temperature storage is extended for the full duration of the target shelf life (Table 1.4).

Table 1.3 Predicted shelf life for refrigerated storage.

Duration of stress test (days) required to predict stability under refrigerated storage (5°C) for the specified duration								
	6 months		1 year		2 years		3 years	
Temperature (°C)	85 kJ/mol	42 kJ/mol	85 kJ/mol	42 kJ/mol	85 kJ/mol	42 kJ/mol	85 kJ/mol	42 kJ/mol
14.5	55.3	100	111	201	221	402	332	603
25	15.1	54	32	108	64	217	97	326
35.5	5.1	30.6	10	61	20	122	31	183
47.5	1.5	16.6	3	32	6	66	9	100
60	0.5	9.2	0.9	18	1.9	37	2.8	55

Table 1.4 Typical stability protocol.

Storage condition	Storage time (months)						
	1 month	3 months	6 months	9 months	12 months	18 months	24 months
40°C/75% RH	X	X	X				
30°C/65% RH	X	X	X	X	X	X	
25°C/60% RH	X	X	X	X	X	X	X

1.2.2.8 Physical Stability

While a detailed discussion on physical stability does not form a substantial part of the guidance, potential changes to the physical attributes of the input drug substances and excipient can also influence the stability of a medicine. For example, as solubility is dependent on the physical form of the drug, critical performance attributes, including bioavailability and therefore the quality safety and efficacy, can be affected.

Similarly physical changes to an excipient present in the formulation may affect the performance of the medicine. It is important to understand the different physical states available to a drug and the associated excipients in the final dosage form. The thermodynamically most stable state is arguably the most critical as other physical states will tend to transform to this state. Similar to chemical degradation reactions, molecular mobility, and any factors that increase molecular mobility in the solid state are critical as to whether a physical transformation of the parent molecule occurs. The Gibbs free energy difference between the different physical states dictates whether the transformation is likely to occur.

Classic examples of shelf life limiting physical changes include crystallization of amorphous drug substance, changes to crystal habit on storage [32], and disproportionation of a salt [33]. If a drug substance can exist as different crystalline forms (polymorphs), each one will have a different free energy depending on prevailing local temperature and humidity conditions, and therefore transformations between polymorphs may profoundly affect solubility (and therefore bioavailability). If a drug exhibits polymorphism, its physical state should be monitored during stability testing (see ICH Q6A [34]). As the presence of water can facilitate molecular movement, it can cause physical form transformation; therefore moisture absorption and moisture content should also be monitored so that any change to hydration status is detected. The kinetics of solid phase transitions is highly complex, making prediction and extrapolation more difficult to achieve.

Selection of the most appropriate physical form involves screening work to understand the number of different physical forms available to the parent molecule and takes place early in the development lifecycle. This is often performed using screening tools after short-term stress storage to accelerate any potential transformation. The screening tools include solid state spectroscopy such as Fourier transform infrared spectroscopy (FTIR), near-infrared (NIR), Raman spectroscopy, X-ray powder diffraction (XRPD), solid-state nuclear magnetic resonance spectroscopy (SS-NMR), and thermal methods including differential scanning calorimetry (DSC) and Brunauer–Emmett–Teller (BET) surface analysis to measure specific surface area and microcalorimetry. Such screening experiments may assess the following aspects:

- Are hydrates or solvates formed in contact with water, solvent, or mixtures of both?
- Are different polymorphic forms available when the parent molecule is recrystallized from a variety of different solvents?
- What physical conditions in terms of temperature and humidity cause a transition between the available forms?
- Does the salt disproportionate?
- Do particle size reduction processes such as milling or micronization have an effect?

The data generated should allow the rational selection of the most appropriate physical form for further development, ideally the most thermodynamically stable option. Where it is demonstrated that different physical forms are available, stability assessment should normally include physical form testing.

In practice automated screening approaches, involving preparation and evaluation of multiple combinations and conditions simultaneously, can be particularly effective. The performance of screening experiments in such a systematic way is an efficient process to check if a potential drug molecule can exist in more than one physical form and to get a preliminary comparative assessment of the stability of drug substance salts or to assess prototype formulations. The sequential nature of degradation studies and excipient compatibility work lends itself to the use of array systems with temperature and humidity control within individual study vials. Using transparent containers the contents can be probed nondestructively using IR or Raman spectroscopy and visible assessment prior to further chromatographic physical forms. These workflow systems can also be used to assess the potential for a molecule to exist in different physical states and examine the physicochemical performance of alternate drug substance salt forms and drug excipient mixtures or formulation prototypes in automated experiments (see Figure 1.5).