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REVIEW ARTICLE IMPORTANCE FORCED DEGRADATION STUDY IN ANALYTICAL METHOD DEVELOPMENT

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ABSTRACT

New medicinal components and products degrade quicker under accelerated circumstances than in normal ones. It proves stability-indicating methods work and reveals the drug's breakdown and final form. It also helps show breakdown product pieces. Forced degrading tests novel pharmaceutical compounds and medical items under stricter conditions than quick degrading tests. These studies show that the molecule is chemically stable, enabling consistent, reproducible formulations. The International Council for Harmonization (ICH) lists irradiation, oxidation, dry heat, acids, bases, and hydrolysis as degradation causes. All of these causes may occur alone or together. The gold standard for forced decline testing is ICH Q1A, QIB, and Q2B. Forced breakdown testing may reveal a molecule's chemical behavior, helping create new formulations and packaging. The regulatory rule is unclear concerning forced decline study technique. This study reviews how forced degradation research has shaped scientific methods. This document highlights their contributions.

Keywords: Stability Study, Forced Degradation Study, Validation, HPLC.

I. INTRODUCTION

The primary objectives of research on forced degradation are to learn about the stability-related features of an active pharmaceutical ingredient (API) as well as its breakdown products and pathways. In addition to determining the drug's sensitivity to hydrolysis across a broad range of pH, the studies in question need to evaluate the drug's sensitivity to hydrolysis. In addition, forced degradation tests are used in order to generate degraded samples, which are then utilized in order to establish testing techniques for the API that demonstrate the API's level of stability. Research on artificially induced population loss may also benefit other areas of development by providing them with more knowledge. The development of analytical methodologies, the construction of formulae and storage conditions, the chemical soundness of manufacturing processes, and the identification of potential API products are all tasks that need to be accomplished. It is to one's advantage to conduct studies on forced degradation at a very early stage in the construction of a system. The reason for this is that these tests offer helpful predictions about the kind of deterioration, which can be used to figure out the best methods to manufacture new molecules. The reason for this is that these tests give useful predictions regarding the type of deterioration. The development of a recipe, as well as the selection of API salts (1).

Many individuals hold the opinion that the forced breakdown research is an essential component of the analytical process involved in the production of small-molecule medicines. Utilizing high-performance liquid chromatography (HPLC) or a single analytical approach that is able to differentiate between the peak of the degradant and the peak of the drug substance or drug product is one way to demonstrate the specificity of an analytical method that indicates stability. In certain circles, this is sometimes referred to as "stress testing." In order to determine an appropriate shelf life for novel therapeutic components or drug products, stability studies need to be carried out in accordance with the guidelines provided by the International Conference on Harmonization (ICH) (Q1A). Studies on a product's shelf life are required as part of several legislative applications submitted to the FDA (2).

Rapid stability (ACC), intermediate stability (INS), and controlled room temperature (CRT) stability are the three types of tests that are often required to be carried out in order to determine how long a drug substance or drug product will be effective once it has been manufactured. Reviewing the intermediate stability and the

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stability at room temperature may take anywhere from 12 to 24 months, whereas accelerated studies can be completed in around six months. When doing a stability research to determine how stable a molecule is, it is normal to anticipate that the drug substance or drug product may alter or break down and produce new molecules, which are often referred to as contamination. This is because the goal of the study is to determine how stable the molecule is. During the forced degrading tests, various forms of stress are intentionally applied with the goal of breaking down the primary component and producing impurities. These impurities should then separate from the primary compound as well as from each other. Therefore, the shelf life of new drug components and/or drug products is estimated using data from forced degradation tests, which is used to anticipate the degradant and decomposed contaminants that may show up during stability studies. In other words, the shelf life of new drug components and/or drug products may be roughly calculated (3, 4).

1.1Stability:

A drug's stability refers to its capacity to retain its essential characteristics after repeated testing or after its expiry date has passed, including its identification, strength, quality, and purity. The quality of a pharmacological substance or final product might vary over time, and stability testing can reveal this shift in a practical way. Stability study requirements are outlined in documents from the FDA, the WHO, the European Medicines Agency, and the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH). The requirement for a stability-indicating test technique (SIAM) is more readily apparent now that ICH standards have been implemented (5).

The FDA defines a stability-indicating technique as one that can demonstrate the changes in key features of the drug material and the drug product over time using a quantitative analytical methodology that has been shown to be reliable. Active components are accurately measured without the use of excipients, breakdown products, process pollutants, or any other potential defects using a technique that demonstrates the stability of the substances. One of the most crucial techniques for determining a drug's stability is high performance liquid chromatography (HPLC). Drug degradation products may be separated, found, and measured with the use of high-performance liquid chromatography (HPLC) methods. In addition, HPLC techniques allow for the detection and quantification of any drug-related impurities that may have been introduced during processing (6).

1.2Importance of stability testing

The fundamental objective of stability testing is to ascertain whether or not the medicine may be used without risk to treat the condition of interest in otherwise healthy persons. If the nitroglycerine pills are not as active as they are supposed to be (up to 85 percent of the strength stated), the treatment could not work, and you might end up dying of angina or cardiac arrest instead. The failure of the product may be explained by its instability as well as its propensity for breaking down into potentially dangerous components. To guarantee that their products continue to be in demand for the longest period of time feasible, producers should do what is in their best interest. When creating a new product, it is essential to carry out stability studies in order to identify the most effective formulation, excipients, and container closure methods. These studies should also define the optimum storage conditions, shelf life, registration dossier, and verification of the stated shelf life and lack of changes. When compared to the accelerated stability study (ACC) (6, 7).

it's probable that the research on forced deterioration would result in the production of more waste from degradation than the ACC did. When creating an analytical technique, it is important to take into account the likelihood of the sample being contaminated or degraded, as well as the existence of known contaminants. It is of the utmost importance to have the ability to differentiate between the numerous peaks, since these cases will show the worst-case situation. When the current method of analysis is unable to discern distinct peaks, an alternative method of analysis should be used. Together with the author's own life experiences, academic materials, such as books and literary citations, and the author's own life experiences are the primary means through which the critical method makes progress (7).

It is generally agreed upon that the book "Practical HPLC Method Development" written by R. Snyder is an authoritative source. Users could benefit from being shown how to produce more clear peak separation via teaching. Methods are considered to be stable-indicating when they can evaluate all samples for their level of

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stability simply by looking at them and differentiating between peaks in stable and unstable samples. Validation of the technique is essential in order to guarantee that the analytical approach may be applied for the goal for which it was designed. If unusual peaks are seen in samples that were not detected under any conditions that may have resulted in induced deterioration, it is possible to assume that the samples were contaminated either during the manufacturing process or during the analysis. Investigations into out-of-service incidents, laboratory investigations, and sample analysis might potentially all benefit from the knowledge acquired by forced decline research (8, 9).

II. FORCED DEGRADATION STUDIES IN STABILITY-INDICATING METHOD DEVELOPMENT

When developing stability-indicating procedures, forced decline, also known as stress testing, demonstrates sensitivity. This is particularly true when only a limited amount of information is available regarding potential degradation products. The process of determining what factors make individual medication components and medicinal products stable on their own is referred to as stability testing. It was not until 1993 that the ICH Guideline Q1A made it an official requirement for regulatory compliance. It is an essential stage in the process of developing a regulatory compliance stability program for both products and medical pharmaceuticals. It is a helpful instrument that is often used in the process of developing medications to establish up techniques for demonstrating stability that yield high-quality stability data (10).

2.1 Outcomes of forced degradation studies

Forced degradation studies offer the following information:

- ✓ Identifying potential degradation routes, identifying potential degradation products,
- ✓ Identifying the inherent stability of the drug's molecule, and
- ✓ Identifying validated stability-indicating analytical techniques

2.2 Regulatory guidelines

Research on forced deterioration is encouraged by a variety of internationally recognized standards. There are times when ICH criteria only apply to new product marketing applications and do not include the period of clinical development (11–13). The following is a list of the guidelines made by the ICH that apply to research that makes use of forced deterioration:

- ✓ ICH Q1A: Stability Testing of New Drug Substances and Products,
- ✓ ICH Q1B: Photo stability Testing of New Drug Substances and Products,
- ✓ ICH Q2B: Validation of Analytical Procedures: Methodology.

Although the Food and Drug Administration (FDA) and the International Conference on Harmonization (ICH) have produced some suggestions for forced degradation testing, these recommendations are not even close to being comprehensive. In particular, the challenges that arise when dealing with drugs that have a low degree of solubility and substances that have a high degree of stability are not well recognized. During stress testing, the question of how much strain should be imposed is not well studied. If the patterns of degradation that are seen in a molecule after it has been subjected to tremendous stress in the process of developing new procedures are not an accurate representation of the conditions that the molecule is likely to experience while it is being stored, their significance may be reduced. Therefore, the limits of the stress test need to be acceptable and should not be too restricted. The level of pressure that is being put on this system is much more critical than the pace at which it is deteriorating. In point of fact, prolonged exposure of some compounds to damaging conditions may result in a little degradation of their properties. There is still a significant amount of ambiguity about the scientific and regulatory procedures that need to be taken at each phase of development (14). Even though the FDA does not need exploratory degradation studies for an investigational new drug (IND) application, they may be helpful in creating stability-indicating procedures that can be used throughout the clinical trials. These methods may be applied throughout the clinical trials. This website offers a useful interpretation and synthesis of the most recent proposals, in addition to providing guidance on the most effective methods for doing research on forced deterioration. This statement provides a synopsis of the general agreement reached by the members of the pharmaceutical industry who were present at the meeting of the analytical research and development steering committee. The sources that are provided are more in the form of

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summaries than complete citations. Indicators of anticipation include both references to the suggestion (15) as well as direct disclosures of information from the recommendation.

2.2.1 ICH Q1A (Stress testing):

In the Q1A guideline published by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), the essential parameters for carrying out stress testing on pharmaceutical substances and products are outlined. It is strongly suggested to do an exhaustive investigation into the results of oxidation, photolysis, temperature, and humidity (more particularly, temperatures more than 50 degrees Celsius for the purpose of accelerated testing). When determining the usefulness of a solution or suspension, it is essential to take into consideration a diverse range of pH values. Last but not least, the technique that was devised for determining the stability of these samples.

2.2.2 ICH Q1B:

In this investigation, Sections II and III provide an in-depth analysis of the forced degradation conditions that were applied to drug material as well as drug product. The studies concerning forced degeneration do not give any specific specifics about the degrees of exposure. Formulations in the forms of solids, solutions, and suspensions are all tested for their photo stability using a variety of methodologies. Next, a method that assures the product's consistency is devised using the offered samples as a basis. During the stability testing, some degradation products may not be identifiable, which would mean that further investigation would be unnecessary.

2.2.3 ICH Q2B:

The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) has published a guideline called Q2B that provides exhaustive criteria for the validation of analytical procedures. It is advised in Section B 1.2.2 (which discusses contaminants that are not readily accessible) to utilize samples produced from forced degradation tests in order to show specificity. This recommendation is made in relation to the topic of contaminants. When determining whether or not an analytical method is effective in demonstrating stability, one of the most important factors to consider is the degree of specificity of the method.

2.2.4 ICH Q3A (R2)

According to the criteria provided by ICH Q3A (R2), it is necessary to identify each impurity in order to evaluate its potential chemical characteristics and the potential risks associated with them. The review of analytical procedures, the construction of reports, the classification and naming of impurities, and the organization of impurities within requirements are all included in the scope of chemical prospects. The safety potentials provide exhaustive recommendations for categorizing contaminants that were either nonexistent in a batch of a new pharmaceutical product or present in very minute quantities within that batch (16).

III. OBJECTIVE FOR FORCED DEGRADATION

a) The purpose is to provide pathways for the degradation of medicinal molecules and drug products.
b) Familiarity with the molecular properties of pharmaceutical substances.
c) In order to provide more elucidation on the constituents of degradation by-products.
d) In order to effectively mitigate concerns pertaining to stability
e) To assess the intrinsic stability of a pharmaceutical ingredient inside a given formulation.
f) In order to illustrate the degradation of the drug ingredient and drug product.
g) The objective is to distinguish degradation products generated by drug products inside a formulation from those generated by non-drug products.
h) To ensure stability, it is important to demonstrate the established character of a procedure (17).
i) In order to develop formulations that exhibit enhanced stability. Additionally, it aids in determining the expiration date of a particular composition.
j) In order to generate a degradation profile that closely approaches the outcomes seen in an authorized stability study conducted according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines (18).

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IV. SELECTION AND PROCEDURES OF FORCED DEGRADATION CONDITION

It is usual practice in the industry to undertake forced deterioration tests in combination with a control sample. These studies are carried out in accordance with the recommendations made available by the International Council for Harmonization (ICH), as well as conventional procedures. In these experiments, the samples are put through a number of different types of stress, including exposure to acid, alkali, peroxide, heat, and ultraviolet light. In spite of the fact that there are no standards for industrial deterioration that are acknowledged by everyone, it is recommended that a range of 5 to 30 percent of deterioration be detected across a variety of stress scenarios. The fundamental objective of stress testing degradation is to correctly reproduce the conditions of stability that are encountered at the temperature of the control room. It is vital to identify higher or lower degradation rates in order to get optimal performance while using the circumstances or concentrations of the reactants. During the analysis of degradation, it is essential to make certain that the mass balance stays within a near proximity to one hundred percent in order to properly account for the range of analytical error margins that might occur (17–19).

In the framework of research pertaining to mass balance, it is essential to calculate the amounts of each degradant and impurity. When doing a research on forced deterioration, it is acceptable to utilize any batch that was not included in the regulatory submission. This is the case even if the study was conducted on a drug. It is best to choose the dosage strength of a pharmaceutical product that has the highest placebo-to-active pharmaceutical ingredient (API) ratio when there are many dosage strengths available for the same product, all of which contain the same active pharmaceutical ingredient (API), but in varied amounts. When variations in placebos are discovered, it is vital to prove that any differences in effectiveness are the consequence of purposeful attenuation of all dosage levels. This may be done by comparing the placebos to a standard dose of the active ingredient. In the process of examining the deterioration of medical products, it is required to conduct tests on both the placebo and the active pharmaceutical ingredient (API) in order to precisely determine the pathways of degradation. This is done for the purpose of gaining more accurate information. When it comes to pharmaceutical drugs that come in a variety of strengths, it is very necessary for research on deterioration to incorporate the presence of different placebos. The degradation criteria for DMF, ANDA, NDA, and IND submissions for regulatory clearance, as indicated in Table 1, are in conformity with current industry standards and have been recognized by the FDA. Additionally, these requirements must be met in order for a submission to be considered for regulatory clearance (18, 19).

Table 1: Suggested Experimental Conditions for Forced Degradation Studies

Degradation Type	Concentration of Reagent	Conditions to be applied	Time	Remarks
Acid	5N HCI	80°C	1 hour	Concentration. condition and time can be changed to optimize degradation.
Alkali	5N NaOH	80°C	1 hour	
Peroxide	10% H_2O_2	80°C	l hour	
Heat/Thermal	80°C	80°C	1 hour	
UV	Expose under UV light at 254 run wavelength	Ambient temperature.	24 hours	Time can be changed to optimize degradation.
Control	NA	NA	NA	NA

It is advised for a consistent final result to carry out the degradation in a solution together with the diluent or mobile phase. Depending on the conditions, degradation may take place either when the substance is in a liquid state or a solid state. It is possible to speed up the study by getting started on degradation studies under harsh circumstances, such as high reagent concentrations and temperatures. It is advised that the temperature and/or the concentration of the reagent be adjusted in the event that the rate of deterioration is more than thirty percent. The results of the first deterioration will serve as the basis for future adjustments to the degradation process, which will be made in order to accomplish a certain objective. It is advised that the pH be

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raised to somewhere around 7.0 in order to extend the useful life of the chromatographic column and limit the amount of degradation that is caused by acid and alkali. In the event that none of the aforementioned conditions result in deterioration, it is possible that it will be required to make use of zinc (Zn), sulfuric acid (H2SO4), and other substances and conditions. It is common practice to use the phrase "exceptionally stable" when referring to a substance's natural resistance to degradation, even when the substance is subjected to unfavorable environmental circumstances. According to the results of the stability test (20), the substance in question does not have a propensity to develop any new contaminants or degradation peaks.

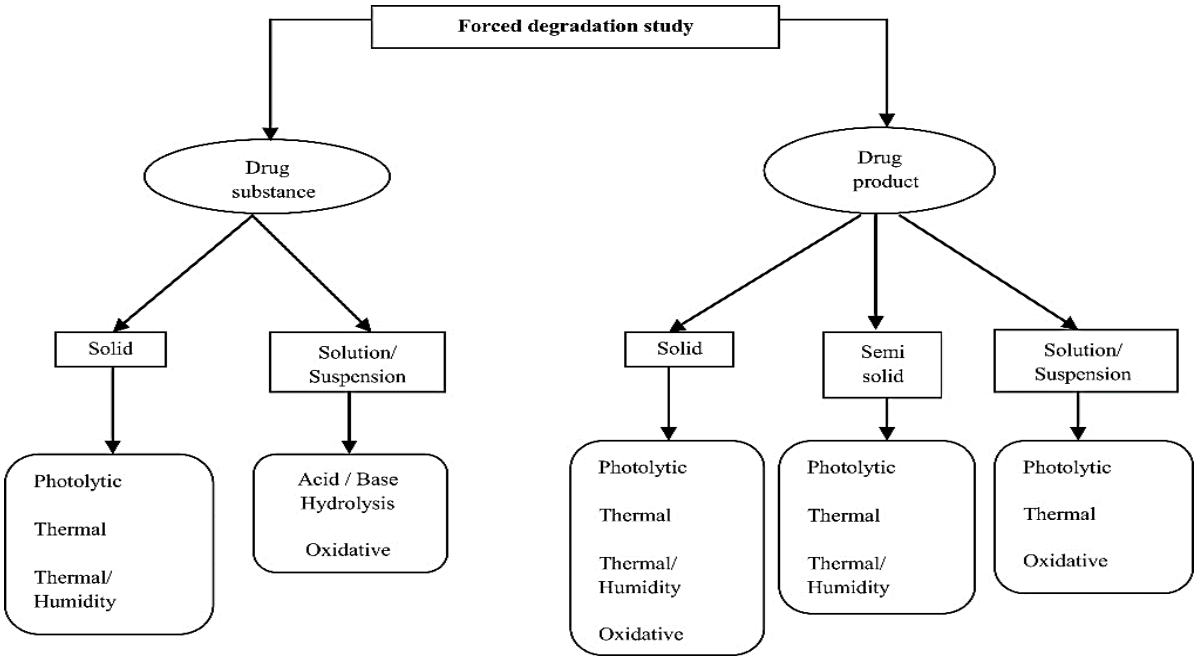

Figure 1: An illustrative flowchart describing various stress conditions used for degradation of drug substance and drug product.

Forced degradation is conducted in order to generate representative samples that may be used in the development of stability-indicating procedures for both drug ingredients and drug products. The selection of stress conditions should align with the product's breakdown under typical manufacture, storage, and use circumstances, which vary in each unique scenario. Figure 1 illustrates a comprehensive methodology outlining the degradation conditions often used for drug substances and pharmacological products.

4.1 Various degradation conditions (21, 22)

4.1.1 Hydrolysis:

The most frequent chemical reaction that may break things down over a broad range of pH is called hydrolysis. When a chemical substance is exposed to water, it undergoes a process known as hydrolysis, in which it is broken down into its component parts. The ionizable functional groups of the molecule are put to use to speed up the process in both acidic and basic hydrolysis. When a substance is brought into touch with an acid or a base, that substance must eventually decompose. The primary waste products are at a level that is acceptable for the situation. When determining the kind and quantity of acid or base to employ, it is important to consider how safe the pharmacological component is. It is recommended to use sodium hydroxide or potassium hydroxides (0.1-1 M) for the breakdown of bases; nevertheless, hydrochloric acid or sulphuric acid (0.1-1 M) is considered to be the most effective option. When some substances do not dissolve well in water, co-solvents may be employed as an alternative. The forced change began at room temperature and proceeded at a quicker rate as the temperature increased. This occurs even if there is no change.

4.1.2 Oxidation conditions:

Hydrogen peroxide is often used in the process of oxidatively forcing a breakdown. Metal ions, oxygen, and azobi-isobutyronitrile are some other things that may be used as radical initiators. Because of the structure of the medicine, it will be able to choose the quantity of the oxidation agent as well as its condition. During the

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process of the therapeutic ingredient decomposing due to oxidation, an electron transfer mechanism takes place.

4.1.3 Photolytic conditions:

The term "photo stability" refers to the capacity of a substance to withstand the effects of being illuminated by light without undergoing any changes. The purpose of photo stability testing is to determine what will happen to a medicine if it is subjected to UV light or strong light for an extended period of time. There is a list of proposed variables for testing photo stability included in the recommendations provided by the ICH. The recommended levels of light for testing drug materials and for lighting solid or liquid drug items are 1.2 million lx/h and 200 W/m2, respectively. The majority of individuals are of the opinion that the most effective range of light wavelengths for photolytic breakdown is between 300 and 800 nanometers. Six million lxh is the maximum amount of light that is recommended. Photo oxidation is a process that may take place when the light stress that leads to the utilization of free radicals. Carbonyls, nitro aromatics, N-oxide, alkenes, aryl chlorides, weak C-H and O-H bonds, sulfides, and polyenes are all examples of kinds of groups that are sensitive to light.

4.1.4 Thermal conditions:

It is recommended that the thermal decay be evaluated using circumstances that are more stringent than those proposed by the ICH Q1A quick testing protocol, such as dry heat and wet heat. It is necessary to conduct testing using both dry and moist heat on solid-state medication components as well as finished medicinal products. It is recommended that drugs in liquid form be heated to a dry heat. It is possible to conduct research at greater temperatures for a more condensed length of time. You can determine out how temperature influences how well something can hold up to heat by using the Arrhenius equation. This equation may be found here.

$$k = Ae{-}Ea/RT$$

Where k is specific reaction rate, A is frequency factor, Ea is energy of activation, R is gas constant (1.987cal/deg mol), T is absolute temperature. Thermal degradation study is carried out at 40-80˚C.

4.1.5 Humidity:

Humidity is a significant contributing element in the formation of possible degradants in both the final product and the active medicinal component. It is often suggested to maintain a humidity level of 90% throughout the course of one week in order to create forced deterioration samples.

V. WHEN TO PERFORM FORCED DEGRADATION STUDIES?

When it comes to the creation of new medicinal substances and goods, the research of degradation that is artificially induced over time is very necessary. The present research is primarily reliant on the third and final stage of the regulatory application procedure. This is in accordance with the criteria provided by the FDA. In order to determine the stability of the pharmaceutical component, it is required to conduct forced degradation studies. These experiments must take place under various pH conditions, in the presence of oxygen and light, and at elevated temperatures and humidity. Studies of forced degradation often center on one single statistic as their primary emphasis. The results are to be summarized in accordance with the requirements of the annual report. There are two main sorts of stability studies, the first being those that are carried out over a longer length of time, and the second being those that are carried out more swiftly. However, shorter studies could utilize conditions that are laxer compared to those used in longer, more in-depth research. Following the completion of the stability testing, the further stages may include pursuing the identification and quantification processes. During the pre-clinical phase or phase I of clinical trials, forced deterioration is highly suggested because it provides researchers with sufficient time to identify degradation products, clarify structure, and elevate stress conditions (21, 22). In addition, it helps researchers better understand the relationship between degradation and stress. In the early stages of manufacturing, forced degradation experiments are used in order to both enhance the production process and make it simpler to choose the most effective stability-indicating analytical tests. The findings of the Food and Drug Administration's testing of artificial aging led them to the conclusion that the results may be trusted:

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5.1 During pre-IND:

During formulation Studies: stability indicating quality attributes, degradation routes. For pre-clinical studies: degradants, identification of toxic components

5.2 During clinical development:

- ✓ Comparing pre-clinical to clinical quality
- ✓ Comparing pre- to post- manufacturing changes
- ✓ In-use stability

5.3 Post-marketing:

Usually studies are not performed but following points considered-

- ✓ Identified new stresses
- ✓ Manufacturing changes
- ✓ Additional indications

VI. CONCLUSION

The examination of forced deterioration is a key field of research that may provide the required information and skill for this goal. The creation of a stability-indicating analytical approach is essential, and the investigation of forced degradation is a fundamental area of research. It is essential to carry out this investigation and provide its results in any regulatory filings that are made. This query makes it easier to determine the characteristics of a drug substance or drug product, as well as the length of time it has left before it goes bad. The findings of this study will contribute, in the long run, to improvements in the product's formulation, production methods, and storage characteristics. The inquiry into forced degradation also helps in the discovery of any contamination that may have occurred during the manufacturing process or laboratory testing. This is because contamination may happen at any point during any of these processes. Because of this, it is very necessary to include the examination of forced deterioration throughout the process of developing the technology and prior to submitting the regulatory dossier to the Food and Drug Administration (FDA) (23). Testing for stability is now widely acknowledged to be the fundamental operation that must be carried out routinely throughout the whole of the pharmaceutical development phase for a brand-new drug or formulation. The phrase "stability-indicating method" (SIM) refers to an analytical methodology that permits the differentiation between active pharmaceutical ingredients (API) and any degradation products that may emerge during the stability testing phase, which is carried out under predefined storage settings. This difference is necessary in order to ensure the product's continued efficacy. When researching novel therapeutic compounds and pharmacological products, it is essential to perform and validate stability-indicating procedures, as well as determine the degradation routes and products of active ingredients. This is done as part of the research process (24).

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