AMJ
ISSN: 0005-2523

ISSN: 0005-2523
Volume 62, Issue 07, September 2022

STABILITY STUDIES AND ITS CONSIDERATION IN DRUG PRODUCT DESIGN: AN UPDATED REVIEW

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Keywords:

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Abstract

The stability data package for a new drug substance or drug product that is required for an application for registration within the three regions of the EC, Japan, and the US is defined by the ICH Q1A guideline. It does not necessary aim to encompass testing for export or registration in other parts of the world. The guideline aims to provide an example of the essential stability data package for novel therapeutic substances and products, while also allowing for a wide range of possible practical situations that may arise due to particular scientific considerations and properties of the materials under evaluation. If there are reasons that can be supported by science, alternative methods can be applied.

Introduction

Stability Studies in New Drug Development

Drug life cycle

A fresh medicinal drug's development is a time-consuming and expensive process. Between 10 and 15 years may pass. A new drug would cost about $500 million to develop. A fresh medicinal drug's development is a time-consuming and expensive process. Between 10 and 15 years may

pass. A new drug would cost about $500 million to develop. [52]. Drug life cycle as shown in fig.1

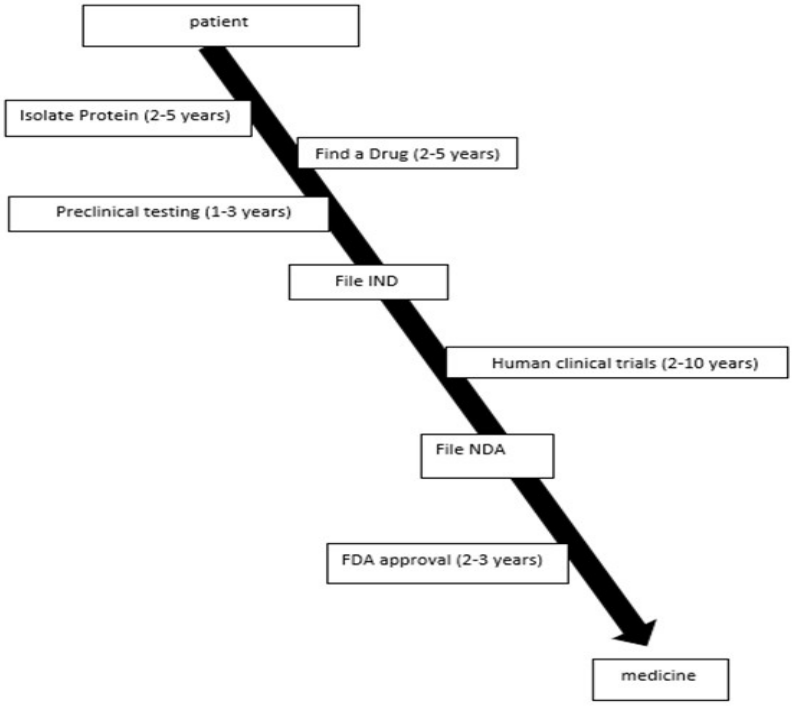

Fig. 1 Depicts the drug's life cycle.

The medicinal chemist concentrates on creating novel chemical entities (NCEs) throughout the drug development process that interact specifically with the molecular targets (such as receptors or enzymes), potentially alleviating disease (1). The synthesis of a number of analogues allows the structural motifs of a top NCE candidate to be adjusted for biological activities and safety. The optimization tools include in vitro and in vivo animal studies, bioavailability (pharmacokinetics), and toxicity analyses (such as biochemical target binding, biomarkers, or animal models) (1,2). To be potential medication candidates, the targeted NCEs must be reasonably stable because they will be ramped up for clinical trials utilizing straightforward formulations. Finally, a commercial drug product containing the final DS is created and submitted for regulatory approval [1].

Biopharmaceutical product development scheme

Steps of biopharmaceutical product development is shown in Fig.2

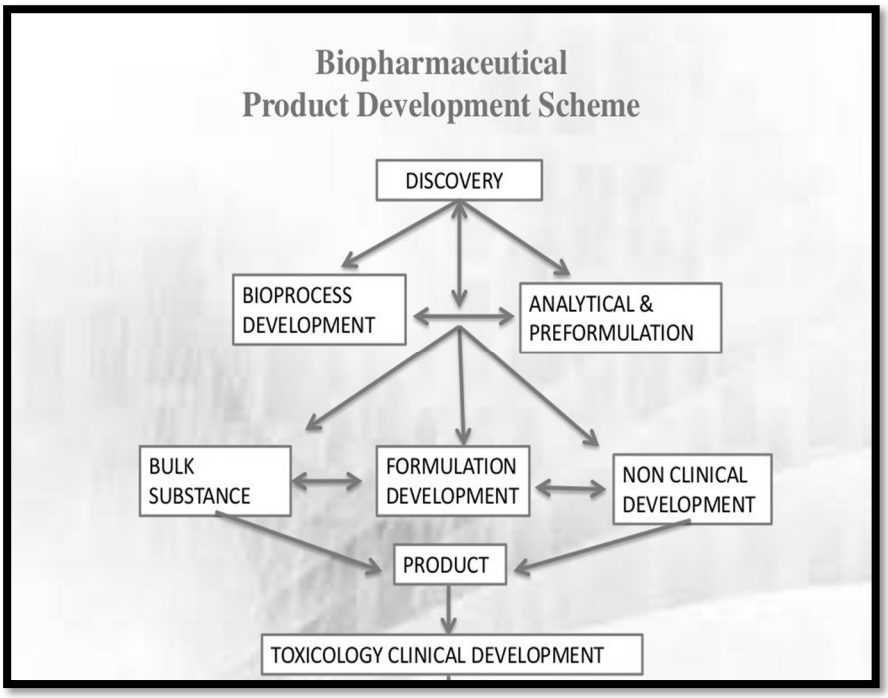

Fig.2 Biopharmaceutical product development scheme.

A multidisciplinary technical development team is formed in the majority of pharmaceutical corporations when an NCE is nominated to the status of a drug development candidate. It is the responsibility of this team to advance the therapeutic candidate through human clinical studies and ultimately to drug approval, manufacture, and commercialization. The team is frequently referred to as the CMC team since it is in charge of tasks that are listed in regulatory papers under the heading "Chemistry, Manufacturing, and Control" (CMC).[2]

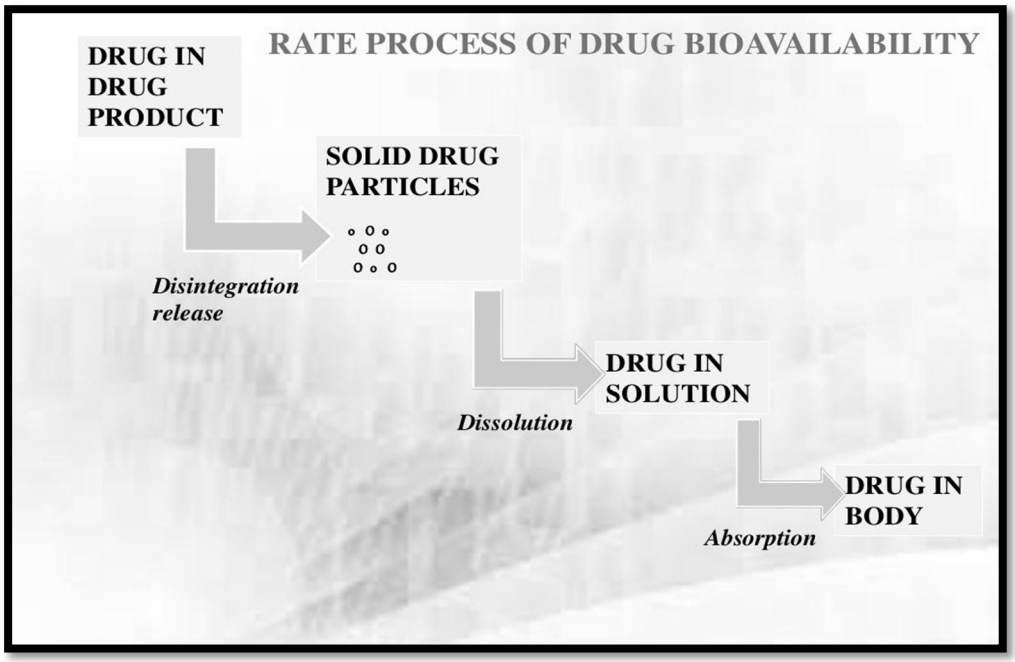

Fig.3 Rate process of drug bioavailability

Clinical trial materials (CTMs) stability studies are carried out to track their CQAs and determine which formulation would produce a viable candidate for regulatory submission. A CTM label does not need to include an expiration date in the United States, but many other nations, including those in Europe, must. Forced deterioration studies, also known as stress studies, are used to question the analytical method's capacity to predict stability. The samples can degrade more quickly thanks to the accelerated research, which call for storage at greater temperatures and humidity levels than typical room-temperature circumstances. Rate process of drug bioavailability as shown in fig.3. It is possible to generalize data from expedited trials to predict the outcomes of a longer-term, controlled-room-temperature investigation.Fig.3 showing rate process of drug bioavailability. The majority of pharmacological drugs show a linear tendency in deterioration. A retest term and an expiration date are given to the DS and DP, respectively, based on the stability data.[3]

Chemistry and Manufacturing Controls

The CMC team typically consists of scientists from a variety of disciplines, including outsourcing, regulatory affairs, supply chain, pharmaceutics, formulation (process chemistry), analytical chemistry (analytical development and quality control [QC]), pharmacokinetics and drug metabolism (PKDM), and project management. The stage of development determines the level of involvement. To assist DS and DP processes, for instance, the analytical development chemist is increasingly involved in the discovery and early stages of development. The later clinical phases for CTM manufacture and regulatory filings, however, are when quality control chemists and regulatory professionals are more active [5].

Among the team exercises are:

1. Carrying out the required synthetic
2. DS process scaling up (process chemistry staff)
3. Thorough characterization of the API, creation and validation of DS and DP analytical protocols, and detection of key impurities and degradation products (analytical development staff)
4. Determining the ideal polymorph or salt of the API in the solid state (analytical staff)
5. Stability studies are being carried out to help clinical development and registration (analytical and QC staff)
6. Researching and designing procedures for creating CTM formulations and the final commercial DP (pharmaceutics staff)
7. Developing commercial requirements and establishing acceptance criteria for CQAs (specifications) to monitor clinical quality (QA and regulatory staff)
8. Developing CTMs (CMC team and outsourcing and project management staff)
9. Assembling the regulatory filings' CMC submission bundle (CMC team and regulatory staff).

Since the drug's dosage is reduced as a result of product instability, undermedication may occur. When a drug or product breaks down, hazardous byproducts could be produced. While being moved from one place to another, the medication has the potential to modify its physical properties. (Because kinetics and stability studies differ, instability may develop as a result of a change in the substance's external appearance. [6]

Types of investigations on the stability of drug substances: [7,8]

The parameters for acceptable levels of physical, chemical, microbiological, therapeutic, and toxicological stability testing are specified in a full pharmacopoeia protocol (USP). Table.1 lists the storage conditions established by ICH Q1A.

Table.1 ICH Q1A-established storage requirements

Label conditions	**Storage Conditions**	**Storage condition**
Controlled room temperature	Long term storage	**25 ± 2^{0}C and 60 ± 5 % RH**
	Intermediate condition	**30 ± 2^{0}C and 65 ± 5 % RH**
	Accelerated condition	**40 ± 2^{0}C and 75 ± 5 % RH**
Refrigerated condition	Refrigerated condition	**5 ± 3^{0}C**
Freezer	Freezing condition	**-20 ± 5^{0}C**

Physical stability

Shape, colour, palatability, disintegration, and susceptibility are still present as are other original physical characteristics. Physical stability is crucial for a product's safety and effectiveness since it can impact how evenly and quickly it releases.[9]

Chemical stability

It is the propensity to remain unchanged or to show no change as a result of reactions brought on by air, the atmosphere, temperature, etc.

Bacterial stability

Microbiological stability is the ability of a drug to withstand sterility and microbial growth. The formulation's antibacterial ingredients continue to function effectively within predetermined limits. This microbiological instability may pose a risk to the sterile drug product.

A stable course of therapy

The therapeutic effects of the medication are unaltered. Toxicological stability: During toxicological stability, there is no discernible increase in toxicity.[10]

Tests for stability procedures

All pharmaceutical products undergo stability testing at various stages of the product development process. Accelerated stability tests, which are frequently conducted at high temperatures and high levels of humidity, are used for early stability testing. The expedited stability studies make it simple to forecast when a medicine will start to lose its effectiveness. In accelerated stability trials, the drug is often kept for a long time. The estimated shelf life of a product is determined using these high temperatures. Stability testing's main objective is to provide the patient with a certain level of fitness and quality acceptability over the course of their availability. They should also be appropriate for the patient's acceptance of the drug. This facilitates the patient's recovery, the patient's acceptance of the medication, and the production of pharmaceutical products with known therapeutic uses. [178] Based on the objectives and actions completed, the four categories of stability testing methods are as follows: 1. 1. Testing for stability in real time 2. testing for stability quickly3. Testing for retained sample stability 4. testing under cyclic temperature stress [11,12].

Stability research advice

The pharmaceutical preparation that will be administered the drug must be as stable as possible for the patient's health, and all products are produced in compliance with the standards advised by the WHO, FDA, and ICH. ICH is essential for developing and marketing the preparations. The "International Conference of Harmonization," which is used to register pharmaceutical products designed for human use, is known by the initials "ICH." The European Commission, Japan, and

the United States all contributed to the creation of the ICH, which was established in 1991. For drug substances and drug products, it created many standards for their quality, safety, efficacy, and multidisciplinary approach (also known as Q, S, E, and M). The secretariat of the ICH is situated in Geneva, Switzerland. These suggestions cover fundamental stability issues, execution stages, and stability data requirements for application dossiers. Later in 1996, the ICH and WHO revised their criteria, and these revisions may be seen in the 2004 publication of the worldwide guidelines for stability studies [13.14].

Regulation Harmonization: ICH Stability Study Quality Guidelines

Understanding the regulatory standards and their intent is crucial to avoiding needless studies because stability testing is costly and labor-intensive. Additionally, laws differ greatly from nation to nation, which has an effect on the price of developing a new drug as well as the time needed for registration before a product may be launched internationally. As a result, the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), composed of representatives from regulatory agencies and scientists from the pharmaceutical sectors, was established at the beginning of the 1990s. The council's job is to standardize the standards for pharmaceutical quality in order to cut down on unnecessary testing and speed up the process of creating new products. The first quality guideline produced by the council was the ICH stability guideline, or ICH Q1, which demonstrated the critical necessity for harmonizing global stability norms.

The World Health Organization (WHO) climatic zones Zones 1 and 2 were covered by the United States, the European Union, and Japan at the time the ICH was created. But numerous nations outside of Zones 1 and 2 joined the ICH or later voluntarily adopted these regulations with varied changes. The current stability guideline (Q1A [R2]) harmonized the storage conditions, frequency of required testing, and the minimal amount of data needed for registration. The stability storage requirements outlined by ICH Q1A (R2) are listed in Table III [15].

Studies of Forced Degradation

Regulations and scientific requirement during the initial method development phase necessitate forced deterioration studies, or stress testing, in accordance with ICH Q1A (R2) and ICH Q2 (R1). Despite the fact that these studies are required by regulations, the guideline does not outline the steps to take or the conditions that should be met. Different organizations appear to use different protocols in practice. Books, papers, and other materials provide a summary of the chemistry underpinnings of medication forced degradation research and best practices [16].

In order to support the early development of the DS stability-indicating methodologies and to examine the main degradative pathways of the DS and DP, forced degradation studies are carried out. For a number of reasons, high-stress conditions are used to put DS and DP in more difficult

circumstances than accelerated situations.

1. To shed light on the mechanisms behind the DS and DP degradation pathways, making it easier to create stable formulations and choose the right packaging
2. Obtaining samples to confirm technique specificity and determining the structure of important degradation products
3. It enable the separation of contaminants, degradation products, excipients, and other interference from the DS
4. To make it easier to quickly build CQAs for the selection or abolition of chosen testing.
5. To quickly detect any DS excipient compatibility issues
6. To produce possible data that could be used to justify specifications.

Studies on forced deterioration are carried out in both solid and solution phases under high temperature, humidity, acid/base, oxidative, and light conditions. An illustration of a set of DS stress situations is shown in Table IV. The generation of a potential level of degradation products that may emerge during manufacture and stability storage is a key objective of forced degradation research. Commonly, forced degradation tests are carried out up to a 5-20% loss of API (18,19). In order to promote method development and prevent secondary degradation products from an unstable degradant, this range is set to create an acceptable number of degradation products (which are not observed under actual stability conditions). The physicochemical characteristics of each DS and DP should be taken into consideration while choosing the conditions [17–20].

Heat Disturbance

By subjecting the drug ingredient to high temperatures in 10 oC increments from 50 to 80 oC, the effect of temperature is examined. The main method of DS degradation in the solid state is thermal degradation [21].

Degradation of Acids and Bases in Solutions

It is important to investigate any potential differences in solution-state degradation mechanisms.

If the drug ingredient isn't soluble in water, you can solubilize it in a little amount (up to 10%) of an organic solvent first, like acetonitrile or methanol, and then add an acid or basic to stress the samples. When choosing a co-solvent, care should be taken to consider the functional groups present in the drug molecule [22].

High concentrations of acid or base should not be used because they are neither practicable nor necessary. A few articles have suggested buffering the pH change from pH 2 to pH 10 over a lengthy number of steps. Establishing a stability model may not be required as a matter of everyday practice, unless it is required for a particular DS or as part of a stress Design of Experiments (DoE) [23].

Photostability

By exposing one representative batch of the DS to the standard light exposure of 1.2 million lux hours of visible light and 200 lux hours of near UV, with storage conditions controlled at room temperature, photostability studies are required and must be carried out to generate primary light-induced degradation products [24].

When there is a change in the DS samples, such as a new synthetic pathway, a different crystallinity form, a different supplier, or a different DP formulation, these tests can be repeated.

In order to gather data on the peak area under the curve, forced degradation samples are commonly assessed using a preliminary HPLC procedure compatible with mass spectrometry (MS) and a photodiode array detector (PDA). Peak tracking, peak purity evaluation, and the detection of degradation products, contaminants, and interferences are all performed using the MS and PDA data [25].

A pharmaceutical laboratory used a four-temperature thermal stressing condition matrix (ambient, 60 ºC, 70 ºC, 80 ºC) for acid, base, oxidative, light, humidity, buffered solution, and prolonged stressed duration as an example of a more comprehensive, elaborate forced degradation protocol to gather data for the majority of their NCEs (up to 21 days). This centralized, automated facility that specializes in supporting forced degradation studies for the development site makes it possible for this sample-intensive technique to be used. The lab used robotics, programmable liquid handling, a system for dispensing powder called "Powderium," automated sample storage and retrieval, and chilled storage for quenched samples [26].

In order to cause a faster rate of degradation than what would be seen under ideal storage conditions, accelerated and stress studies are carried out. Results from these experiments are utilized to determine the real degradation pathways, estimate the stability profiles of the DS and DP under long-term storage circumstances, and show the inherent stability of the DS. The results of these studies may be used as supporting data in regulatory document packages, so it is advised that they be carried out under GMP guidelines. To confirm the retest date of the DS and expiration date of the DP, full shelf-life tests are still required [27].

While forced degradation studies for NCEs are frequently discussed in great detail in NDA applications, they are frequently insufficient in ANDA applications and may lead to regulatory problems. The impurity profiles, for instance, might not be completely derived or sufficiently discussed (20). Additionally, the labelling for generic drug products needs to match the reference listed drug's (RLD) and, if necessary, a compendial monograph [28].

Stable storing

In humidity stability chambers, stability samples are maintained at a constant temperature. These chambers must be maintained within 2 ºC and 5% RH for chambers operating at 25 °C/60% RH, 30 °C/65% RH, and 40 °C/75% RH, according to the ICH Q1A (R2) regulation. With ambient humidity, the refrigerated condition is maintained at 5 ºC to 3 ºC (2 to 8 ºC) (monitored but not controlled). The temperature and relative humidity of these chambers are continuously monitored by sensors. Electronic recorders or chart recorders with backup power are used to capture these data. An alert system will be used to record excursions. Investigations must be carried out to determine the root of the problem and the effect of the stored samples when the chambers are out of tolerance (see above) [29].

To ensure that sample removal is monitored and regulated, the stability chambers are properly certified, maintained, and only accessible to authorized people. During audits, maintenance and service records must be accessible for inspection. To prevent problems that may influence sample storage and data integrity, downtime must be kept to a minimum and a backup strategy must be created. To keep track of sample storage and disposal at all times, a chamber inventory procedure that is implemented annually is also required [30].

Strategies for Stability Studies to Quicken "First-in-Human" Clinical Trials

For the majority of pharmaceutical businesses, reducing "Time to Market" is a crucial strategy [31]. It is customary to perform preliminary accelerated stability studies on the Good Laboratory Practices (GLP) toxicological DS and prototype DP batches to provide supporting data for quicker IND submissions, given that regulatory agencies expect to see three months of stability data in IND filings to enable Phase I clinical trials. As demonstrated in Table VII, early-phase stability studies are frequently brief, and the research circumstances vary on the location of the clinical trials. The analytical methods are typically not fully validated during Phase I, but studies on specificity, accuracy, linearity, and precision should be finished. Pharmaceutical companies are able to begin Phase I clinical trials as soon as possible after the nomination of the drug candidates thanks to these time-saving techniques [32].

As formulations are being developed, characterization studies of the API and DP are ongoing. According to GMP rules and the ICH Q1A (R2) guideline, it is advised that the forced degradation studies be repeated prior to the release testing and the start of the official stability studies (8). There is discussion elsewhere of conventional stability protocols that are provided for various dosage forms at various stages of medication development (6,7). The stability part of the NDA or ANDA contains the findings of the formal stability studies that were used to establish the shelf life of the drug products [33].

Tools for Predicting Product Expiration

A final product's expiration date is determined using stability data in accordance with US FDA Good Manufacturing Practices rule 21 CFR 211.137. (21). A potential expiration date is calculated using the data from the accelerated condition, however testing during the full shelf life is required to confirm the allowed expiry [34].

In this section, we go over several illustrations of practical software applications and statistical techniques for assessing stability data and accelerating stability studies for determining product expiry.

The majority of tools are science- and risk-based, and they have solid statistical foundations that follow the QbD and DoE principles, which are supported by regulatory organizations for pharmaceutical development [35].

Modern Predictive Approaches and Methods

The Accelerated Stability Assessment Program (ASAP), which employs a modified Arrhenius approximation, is one extensively used method. This method applies extrapolation to lower temperatures and humidity for longer time periods by using degradation kinetics under a few stressful circumstances in 1-2 weeks. The short duration of these studies and the utilization of less resources make this method advantageous. This model's correctness relies on a first-order process, which is frequently the case for degradation based on hydrolysis. The drawback is that the assumed kinetic model, which extrapolates three variables at once—time, temperature, and humidity—limits the degradation to less than a percent. When the DS and DP have a straightforward kinetic pathway and temperature and humidity are the main stability variables, these drawbacks are reduced. Another issue is that the linear model could not be accurate if the kinetic route is complicated, nonlinear, or involves physical changes. The drug to excipient ratio of the formulation was recently optimized based on moisture content, and appropriate packaging was chosen based on its thermal and moisture-barrier properties. This strategy has acquired acceptance from numerous regulatory organizations [36] and is mostly used to determine the expiration for therapeutic products.

The Predictive Characterization Study (PCS), which develops reliable stability models quickly using a semi-empirical design space, is another effective approach. It is a methodical study that assesses the product data of samples exposed to various storage conditions in order to develop predictive stability models and establish the design space and control strategy based on the QbD concept, including setting specifications and choosing suggested container-closure systems. Many regulatory organizations also approve this strategy [37].

Compared to forecasts made using the conventional extrapolation method, improved modelling

tools have made it possible to make stability predictions with shorter timescales. These models are used to improve understanding of the critical elements that affect the quality of the DS and DP, as demonstrated in empirical science and risk-based approaches described in ICH Q8-Q11, in addition to giving a more accurate way to support an expiry assignment. Large pharmaceutical companies with better modelling resources and expertise frequently use these strategies. In order to employ risk-based predictive stability data for setting up shelf life to help clinical development, a regulatory template has been given to standardize on key components [38].

Table.2 Comparing the major divisions of the digestive tract's anatomical lengths in rats and humans [39].

ICH CODES	Guideline Titles
Q1A	Stability testing of new drug substance and products (second revision)
Q1B	Photo stability testing of new drug substance and product.
Q1C	Stability testing of new dosage form.
Q1D	Bracketing and matrixing design for the stability testing of drug substance and product.
Q1E	Evaluation of stability data.
Q1F	Stability data package for registration application in climatic zones III and IV
Q5C	Stability testing for biotechnological /biological product.
Q6A	Specification: test procedure and acceptance criteria for new drug substance and new drug product: chemical substance.
Q6B	Specification: Test procedure and acceptance criteria for new drug substance and new drug product: biotechnological/biological products.

Study protocol for staff

Stability testing is a step in the process of developing a medicine. The stability results from the stability studies are used to determine storage conditions and packaging materials for the majority of prepared, formulated items. The shelf life of the chemical is determined using the stability studies [40]. The stability investigations must follow certain stability methods, and there must be a written record with clear instructions for the regulated and well-controlled stability studies. The protocol could change depending on the type of pharmacological drug because different packing containers are needed for different formulations. Both commercially accessible pharmaceuticals and recently created drugs may have an impact on the processes. The protocols should take into account the regions that the ICH has recommended. A protocol for a stability study should contain the following information: 2. The quantity of batches. Packaging and fasteners 3. Time point sampling is the fourth, storage container orientation [41].

Equipment Stability study

The equipment used for stability testing is called a stability chamber. These customized environmental chambers may simulate the storage environment and allow the assessment of product stability through real-time, expedited, and long-term procedures. There are walk-in and reach-in options available. Smaller chambers are chosen for testing that needs to be finished quickly because the retention duration of objects in these cabinets is significantly reduced, even though walk-in chambers are suited for long-term testing. These chambers or rooms are built and certified to ensure that every sample within is exposed equally to the specified conditions. These chambers need to be durable and dependable because they will be in operation continuously for up to five years. They are equipped with the necessary recording, security, and alarm systems. Additionally, temperature and humidity control are optional when using photo stability chambers. Two different kinds of light sources are frequently employed in photo stability chambers: one is a combination of near-UV and cool white fluorescent tubes, and the other is a sort of artificial daylight lamp, such as a xenon or metal halide. It is necessary to reach a cumulative exposure of 1.2 million lux hours. To measure the brightness of visible light, one uses a lux meter. The number of exposure hours necessary is calculated. [42]

Taking into account when designing a drug product

Chemical or biological substances Individual chemicals or a blend of multiple components Conventional treatments were used in the past for treatment. Diseases are currently treated at the molecular level [43].

Target medicines

A protein molecule, receptor, enzyme, transport molecule, ion channel, tubulin, or immunophilin can all be targets.

Types

There are four fundamental strategies that are typically used in the creation of pharmaceuticals:

1) Drug design that is indirect or ligand-based.

2) Direct drug design or structure-based drug design.

3. Reasonable Drug Development.

4) Computer-assisted drug design.

Mechanics-Based Drug Design

2) Drugs may be developed particularly to interact with the target molecule in a way that prevents the development of the disease when the target molecule(s) are identified and the disease process is understood at the molecular level [44].

Designing Drugs with Structure

1) The initial approaches to drug design.
2) assisted in the search for new medications.
(3) Calculations are utilized to uncover more information about the electronic properties and structural dynamics of ligands.
4) There are fundamentally two types of structure-based drug design [45]:
1. Ligand-based
2. receptor-based
Drug Development Using Ligands:
In the first category, a large number of potential ligand molecules are screened, and ligands for a given receptor are "discovered". This procedure is commonly known as "ligand-based medication design." Synthetically producing novel lead compounds is easier[46].

Docking
In docking, the "optimal" chemistry between two molecules is sought after. It involves looking for the correct lock key. Assuming there are two biological molecules, determine whether or not they "interact," and if they do, what is the complex's orientation that maximizes "interaction" while minimizing its overall "energy"?

The idea is to be able to search a database for chemical structures and receive a list of all molecules that might interact with that structure [47].

Receptor-based drug design
Receptor-based drug design is another kind that focuses on "generating" ligands. Piecemeal assembly occurs over time to produce ligand molecules inside the confines of the binding pocket. These pieces could be isolated atoms or little pieces of molecules. The capacity to propose novel structures that are not included in any database is the main advantage of such a technique.[48]

Crystallization using X-rays
When learning about mechanistic drug design, one should start with the molecule that has already crystallized. This provides the essential coordinates needed for data management by computer modelling tools, in order to establish a molecule's structural details [49].

Atomic magnetic resonance
NMR uses radiation that is much more delicate. Examine the molecular make-up of the liquid phase that is more mobile. Three-dimensional data will be gathered. examines intricate interactions between large and tiny molecules [50].

Homology modelling
Building an atomic-resolution model of the "target" and a three-dimensional experimental model

of a pertinent homologous protein is known as homology modelling, also known as comparative protein modeling [51].

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