Stability program in the development of a medicinal product

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Introduction

A medicinal product is designed to possess certain desirable properties of which the stability is of major importance.

When the product is administered by the specified route, the active substance should achieve the required rate of absorption and extent of bioavailability.

The product itself should be efficacious, safe, and acceptable to the patient; it should be convenient in use and **stable**.

Introduction

The stability of a product relates to its resistance to the various chemical, physical, and microbiological reactions that may change the original properties of the preparation during transport, storage, and use.

Other criteria of stability are the effects of such changes on the fitness of the product for use as a medicine.

Criteria for acceptable level of stability

Type of stability	Conditions maintain through the shelf-life of the drug product
Chemical	Each active ingredient retains its chemical integrity and labeled potency, within the specific limits .
Physical	The original physical properties , including appearance, palatability, uniformity, dissolution, and suspendability are retained.
Microbiological	Sterility or resistance to microbial growth requirements. Antimicrobial agents that are present retain effectiveness within the specific limits.
Therapeutic	The therapeutic effect remains unchanged.
Toxicological	No significant increase in toxicity occurs.

What is the goal of stability program?

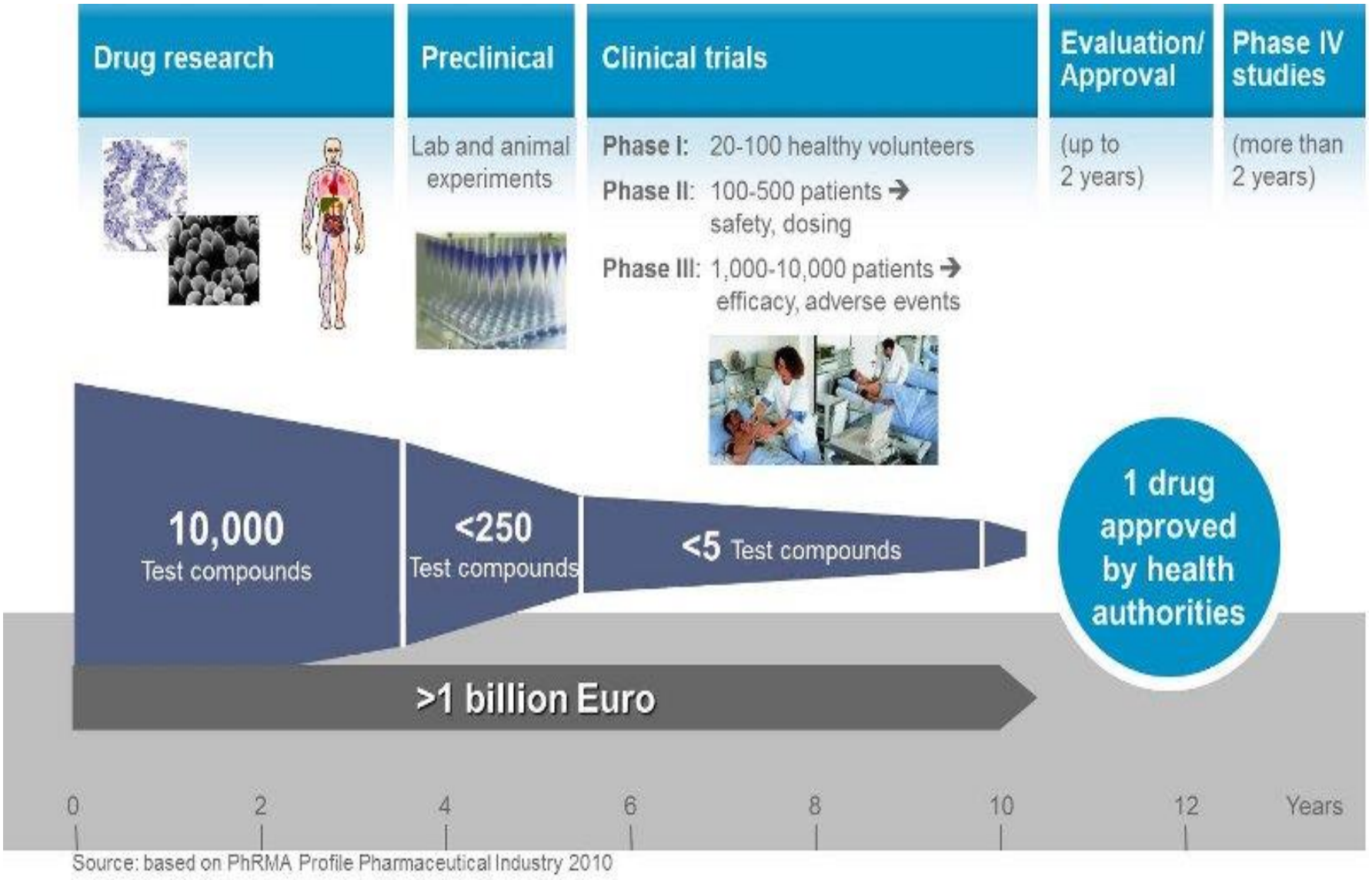
The goal of a stability program is not uniquely defined, but depends on the stage of the development of the product in question.

Drug development

Drug development is the process of bringing a new pharmaceutical drug to the market once a lead compound has been identified through the process of drug discovery.

It includes pre-clinical research on micro-organisms and animals, clinical trials on humans, and may include the step of obtaining regulatory approval to market the drug.

Drug development



Source: based on PhRMA Profile Pharmaceutical Industry 2010

The Role of Stability in Drug Development

- Stability studies play a central role in drug development

- Permit understanding of the molecule

  Mechanism of instability: chemical (labile centers, external factors, degradation) and physical (polymorphs, particle size/surface area other attributes as re-suspendibility and aggregation)

- Essential for developing analytical methods
- Essential for selecting packaging for drug substance and drug product

  Linked to mechanisms of instability (protect from light and moisture, potential drug absorption and adsorption to container closure), container orientation and potential for leachables (container, closure, glue and ink)

- Essential for choosing storage conditions for drug substance and drug product.

Definitions

Absorption

Assimilation of molecular species throughout the bulk of the solid or liquid is termed as absorption.

Adsorption

Accumulation of the molecular species at the surface rather than in the bulk of the solid or liquid is termed as adsorption.

Extractables

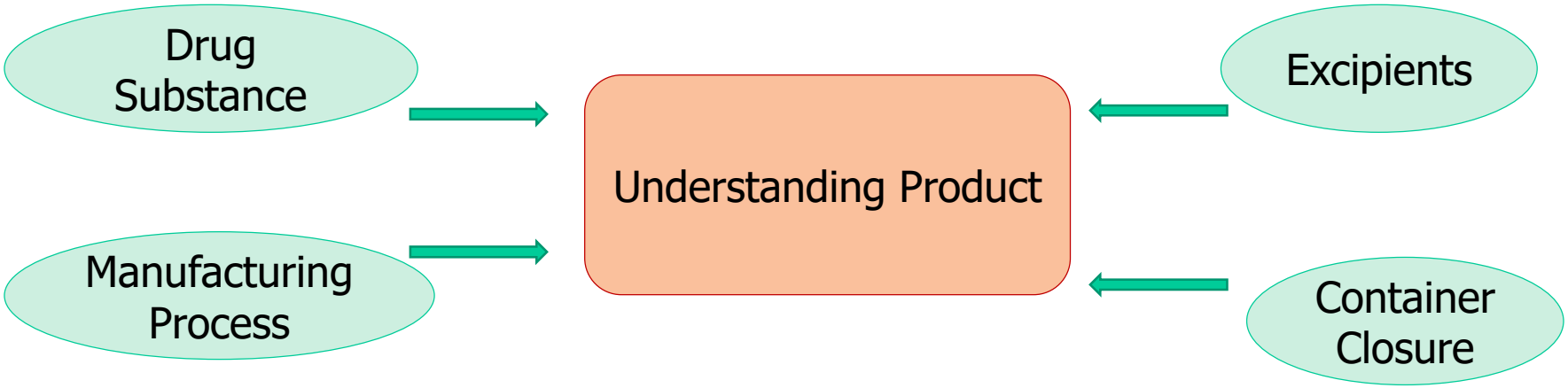
Compounds that can be extracted from the container closure system when in the presence of a solvent.

Leachables

Compounds that leach into the drug product formulation from the container closure as a result of direct contact with the formulation.

Stability Quality by Design

Pharmaceutical product stability is a function of:



Pharmaceutical Quality by Design (QbD)

In contrast to the traditional regulatory system of quality by testing (QbT), QbD is a systematic, scientific, risk-based, holistic and proactive approach to pharmaceutical development that begins with predefined objectives and emphases product and processes understanding and process control.

It means designing and developing formulations and manufacturing processes to ensure predefined product quality objectives.

Quality by Design

- identifies characteristics that are critical to quality from the perspective of patients,
- translates them into the attributes that the drug product should possess, and
- establishes how the critical process parameters can be varied to consistently produce a drug product with the desired characteristics.

Pharmaceutical QbD

In order to do this the relationships between formulation and manufacturing process variables (including drug substance and excipient attributes and process parameters) and product characteristics are established and sources of variability identified.

This knowledge is then used to implement a flexible and robust manufacturing process that can adapt and produce a consistent product over time.

Thus, some of the QbD elements include:
– Defining target product quality profile
– Designing product and manufacturing processes
– Identifying critical quality attributes, process parameters, and sources of variability
– Control manufacturing processes to produce consistent quality over time.

Pharmaceutical QbD

Using QbD, pharmaceutical quality is assured by understanding and controlling formulation and manufacturing variables.

Product testing confirms the product quality.

It will transform the Chemistry, Manufacturing, and Controls (CMC) regulatory review (based on the traditional regulatory system of quality by testing), into a modern science-based pharmaceutical quality assessment.

Goals of the stability in preformulation

At the very onset of development it is desired to know:

a. what the inherent stability of the drug substance is and
b. what interaction with excipients can be expected.

On the analytical side in preformulation

The stability program is usually supported by an analytical research group, which is responsible for the stability indicating assay that goes into the NDA (New Drug Application) or equivalent.

This also applies to the toxicology formulations as a recommendations for stability of the drug substance in the vehicle used in the animal trials.

Stability-indicating assay

The stability-indicating assay is a method that is employed for the analysis of stability samples in pharmaceutical industry.

With the advent of ICH guidelines, the requirement of establishment of stability-indicating assay method (SIAM) has become more clearly mandated.

The guidelines explicitly require conduct of forced decomposition studies under a variety of conditions, like pH, light, oxidation, dry heat, etc. and separation of drug from degradation products.

The method is expected to allow analysis of individual degradation products.

Goals of the stability in preclinical formulation

In the preclinical formulation phase the choice of formula is the primary goal.

This is an important aspect, since this will be the temporary formula framework which is entered into IND (Investigational New Drug Application) or equivalent.

Goals of the stability in clinical formulations

In the new product stability phase, clinical batches are involved and the goal of the stability program is:

a) to ascertain that the batches tested in the clinic are stable, and

b) they serve to support for the final NDA.

Analytical support comes from analytical research up until this point, and at NDA time from routine QC (quality control).

Goals of the stability in product monitoring

In the product stability monitoring, the goal is:

- to fulfill the commitment part of the NDA and

- to adhere to GMP requirements that a program exist to ascertain stability of marketed product.

This is spelled out in the guidelines that the first three market batches and at least one batch per year be tested on stability.

Goals of the stability in post-NDA changes

Finally, it is obvious that a marketed product could be undergone to substantial changes in:

- formulation, supplier, container-closure

- new manufacturing facilities,

and the goal is to show that the change does not adversely affect stability.

Post-NDA changes are usually handled by a production support group and QC on the analytical side.

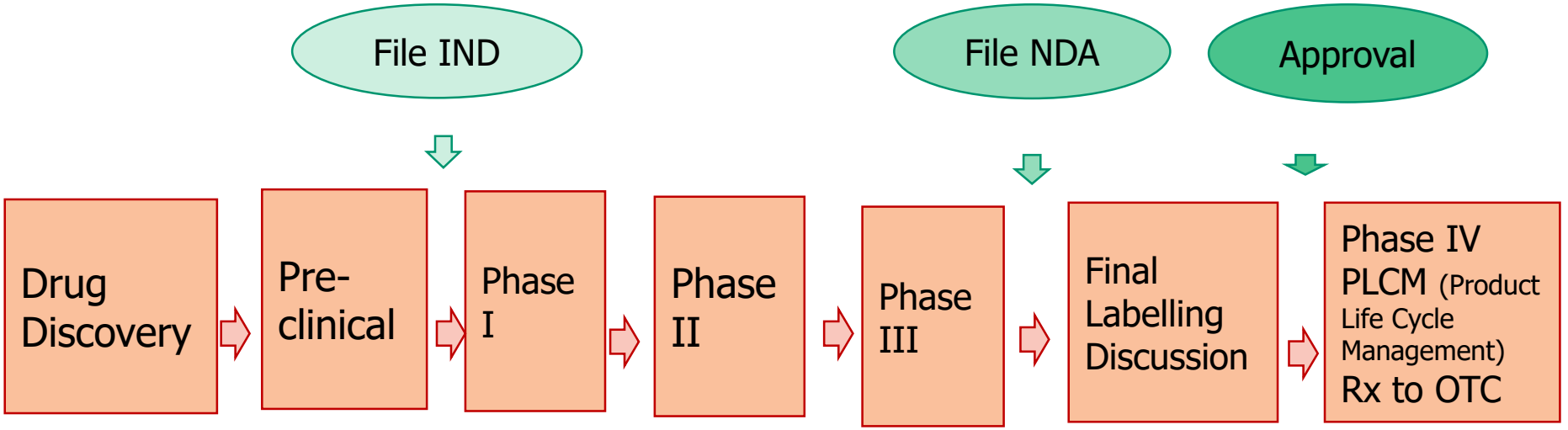
Stability functions

Hence, stability in itself does not define a single function.

There are functionally five types of stability functions:

1. Preformulation
2. Preclinical formulation
3. Clinical and NDA formulation
4. Commitment and product monitoring
5. Post-NDA change of formulation.

Stability studies during drug product Lifecycle



Stability studies to support formulation development and clinical studies

Stability studies to support marketing application

Stability studies to monitor product quality and support post approval changes

Preformulation

The early phase of development of new drug includes the conveyance of information relating to the formulation design to the formulators.

The most salient aspects are:

a) sensitivity to moisture, heat, light and oxygen,

a) interaction probabilities (compatibility with excipients),

b) optimum pH (when in solution or suspension).

Heat-stability program

Accurately weighed samples of drug substance are placed into appropriate containers.

The following are typical variations studied:

1) drug substance as is

2) drug substance with moisture added as water (approximately 5%)

3) drug substance equilibrated at high relative humidity (75% RH or greater)

4) overlaying the headspace of the container with nitrogen versus air prior to sealing.

Typical short-term stress stability program

The containers are sealed and placed at several temperature conditions and testing according to a typical scheme shown in the table.

Temperature	Duration[a] (weeks)			
	1	2	4	8
Refrigeration	(x)	(x)	(x)	(x)
Room temperature	(x)	(x)	(x)	(x)
55°C	x	x	x	x
75°C	x	x	x	
95°C	x	x		

[a] Parentheses indicate samples pulled but not assay (as controls)

Light stability program

The standard conditions for photostability testing are described in ICH Q1B guidelines.

Exposure samples with a validated chemical actinometric system (Option 2) to both

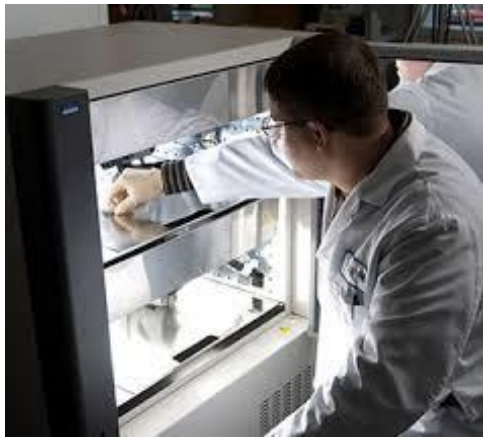
- the cool white fluorescent and
- near ultraviolet lamps for appropriate duration of time.

Exposure of the drug substance in a open petri disches to 900 footcandles (fc) of illumination for 4 weeks is adequate to provide some idea whether light protection is required.

Humidity stability program

The dependence on the ambient moisture is known by exposing the drug substance to different relative humidity conditions using laboratory desiccators (containing saturated solutions of various salts), placed in a oven at a constant temperature.

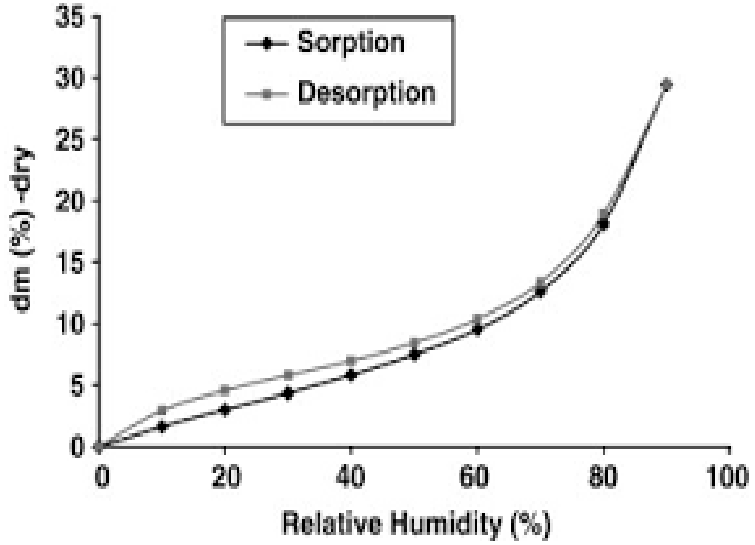
These data are useful in determining if the material should be protected and stored in controlled low-humidity environment.



Humidity stability program

Dynamic vapor sorption (DVS) is a gravimetric technique that measures how quickly and how much of a solvent is absorbed by a sample: such as a dry powder absorbing water.

It does this by varying the vapor concentration surrounding the sample and measuring the change in mass which this produces.



Effect of oxygen

The stability investigation of the sensitivity of drug substance to atmospheric oxygen can often be combined with elevated temperature studies comparing samples under inert gas and air.

Samples are placed at 70-75°C for a week and analyzed.

pH-stability profile

A pH stability profile experiment is performed with solution samples between pH 2 and 12 at a selected elevated temperature.

Analytically prepared solutions, close to the desired concentration, are prepared used buffer solutions within selected pH range and filled in ampuls (air and nitrogen headspace).

The samples are maintained at a specific temperature between 55 and 95°C for two weeks.

Autoclaving studies

Since autoclaving is a preferred means of achieving the sterility of the solutions, an early determination of stability to autoclaving should be made.

Ampouls containing solutions at the optimum pH range previously established are exposed to autoclaving conditions of 121 °C at 2 bar for 20, 30, 45, and 90 minutes.

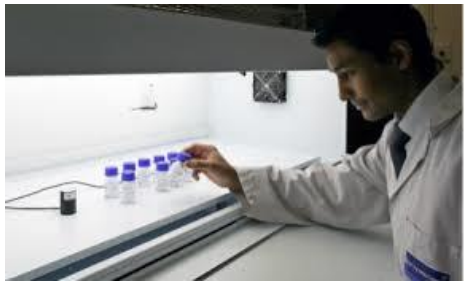
Drug excipient compatibility

One of the objective of a preformulation study is to identify compatible, potentially useful excipient so that a stable formulation can be developed quickly.

Generally, several binary mixtures of a drug and various excipients (generally 1:1 ratio, but lubricants 10:1) are prepared and subjected to:

- thermal analysis (DSC) and/or
- stress studies (e.g., 55°C for 2 weeks)

  before analysis by chromatographic method.

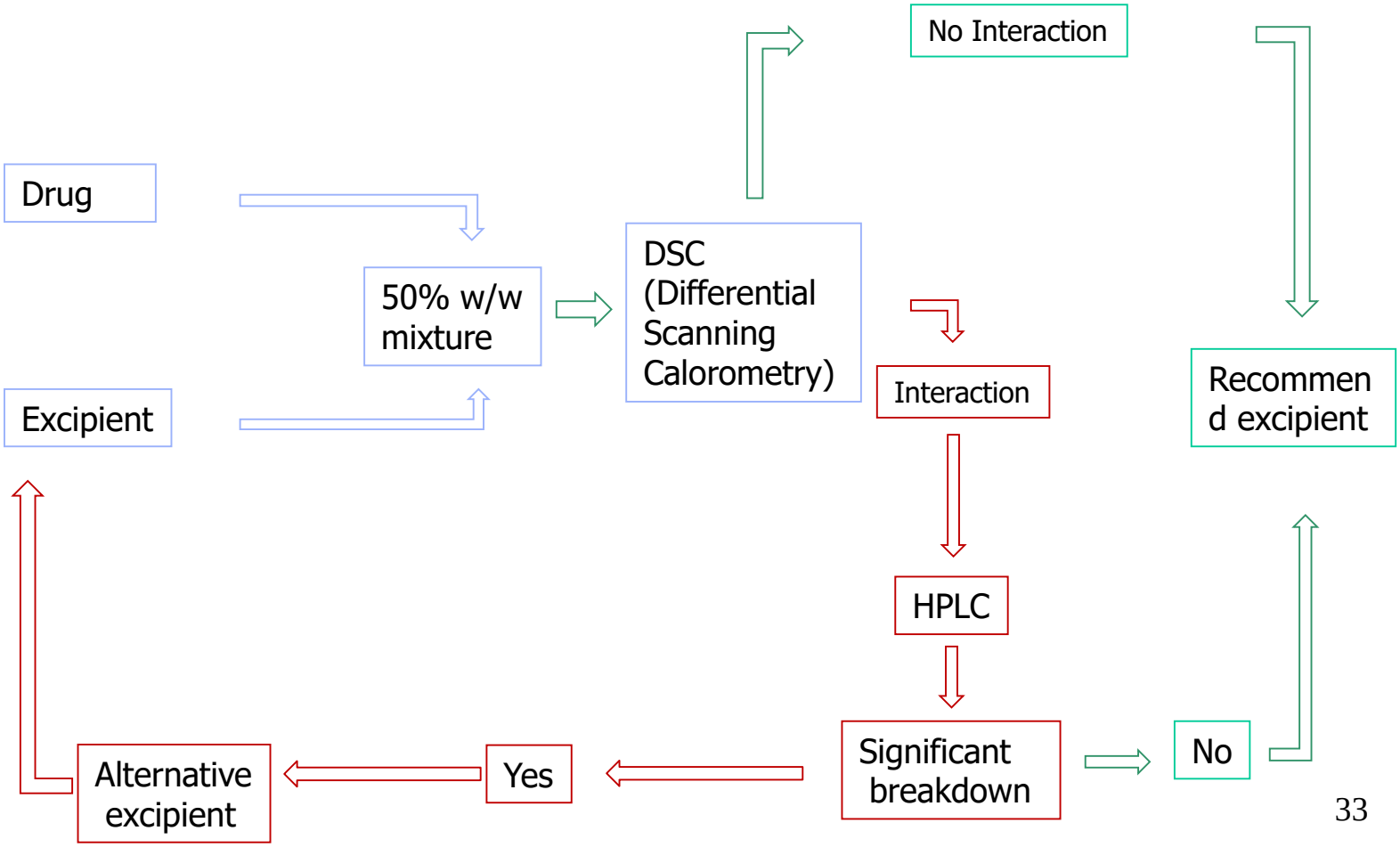


Also the presence and absence of oxygen, light, humidity can be investigated.

From an experience of verification of compatibility with excipients of twenty active principles showed that 10 days at 55 °C corresponded to 24 months of storage at 25°C for most of the tested substances.

Drug excipient compatibility

Scheme to identify chemically compatible excipients using DSC with confirmatory HPLC



What is important in this phase?

A good communication between preformulator and formulator as well as both with analyst is essential.

The development of a drug dosage form is a team effort, and the responsible of the project development should ascertain this.

The best way of communication, as long as there is harmony among people.

Preclinical formulation

Formulation is thought by many to be an art, and there are certain aspects of it that are.

Each company has the old–timer type of formulator who has a "feel" for what done with a formula.

Such persons are worth their weight in silver, and if coupled with a knowledgeable formulation scientist become twice their weight's worth in gold.

Again, teamwork and good communication are the key words.

Preclinical formulation

The challenge of the formulator is to develop the initial and final dosage forms (selecting the most stable) to the highest quality in the shortest time.

It is essential that the formulator understand and effectively utilize the preformulation information on stability.

If the drug substance is, e.g., incompatible with magnesium stearate, he cannot take the stand that it is impossible to formulate the product without magnesium stearate. There simply has to be an attempt.

He must also stay in touch with the preformulation group, if he thinks that other raw material may be of advantage in the formula.

Clinical formulation

After a product has passed the phase I (safety and appropriate dosage), clinical batches limited to small and medium size are made by "clinical manufacturing group", that establishes what the formulation characteristics (specifications).

The required stability aspects of clinical are simply to ascertain that each clinical batch is within specifications for the duration of investigation.

Clinical formulation

ICHQ1A guidelines

Many companies place every clinical batch on stability according ICHQ1A guidelines.

Conditions Minimum Time Period at Submission

- Long term testing 25°C ± 2°C/60% RH ± 5% 12 Months
- Accelerated Testing 40°C ± 2°C/75% RH ± 5% 6 Months

Where 'significant change' occurs due to accelerated testing, additional testing at an intermediate condition e.g., 30°C ± 2°C/60 percent ± 5 percent RH should be conducted.

Clinical formulation

ICHQ1A guidelines

'Significant change' at the accelerated condition is defined as:

1. A 5 percent potency loss from the initial assay value of a batch;
2. Any specified degradant exceeding its specification limit;
3. The product exceeding its pH limits;
4. Dissolution exceeding the specification limits for 12 capsules or tablets.
5. Failure to meet specifications for appearance and physical properties e.g., color, phase separation, resuspendibility, delivery per actuation, caking, hardness, etc.

Clinical formulation

Others use skip-lot sampling (only a fraction of the submitted lots are inspected to demonstrate that the quality of the submitted product is very good).

They place the first clinical batch on accelerated and room temperature stability storage, and, if no adverse stability results are gathered, they simply apply a skip-lot principle and place every nth batch on stability and keep stability room temperature retention on remaining lots.

Clinical formulation

Skip-lot sampling is somewhat dangerous practice, because in the early phases there may be substantial batch-to-batch variation.

So at least some accelerated studies on more batches (e.g. two weeks at 55°C) would be advisable.

Also, clinical batches may provide very valuable backup stability data that will help in the argument the FDA applies against obtaining expiration periods by extrapolation of the data of the final formula.

Late clinical and first pilot batches

In the late phase III clinical, larger batches are made of the product with the formulation which is become firmer and few changes are anticipated.

Close to a NDA submission, a scale-up pilot batch (e.g. half-size) will be made in production equipment and formulation changes must be expected.

Stability data on the final batches are analyzed statistically to set a suggested expiration period for the NDA.

Marketed product stability

At the time the NDA is filed, the large clinical and the scale-up batches are still fairly young (usually data from these batches not in excess of 18 months).

The FDA does not allow extrapolation, but an extrapolated expiration date is usually calculated and then requested.

The FDA often grants two years. There is then the commitment clause, that the follow-up stability be carried out.

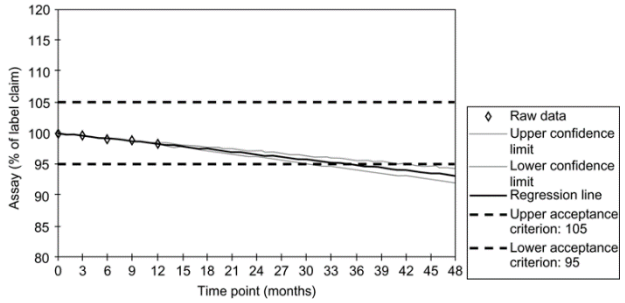
Extrapolation

Extrapolation is the practice of using a known data set to infer information about future data.

Extrapolation to extend the retest period or shelf life beyond the period covered by long-term data can be proposed in the application, particularly if no significant change is observed at the accelerated condition.

Any extrapolation should be performed such that the extended retest period or shelf life will be valid for a future batch released with test results close to the release acceptance criteria.

An extrapolation of stability data assumes that the same change pattern will continue to apply beyond the period covered by long-term data.



An advise for marketed product stability

If smaller problems exist with the formula, it is usually wise to ask for approval of NDA with the formula in hand, and after approval submit an amendment.

This would have had to be submitted to equivalence testing relative to both stability and biopharmaceutics.

Routine monitoring

In the marketed product stability the first three to five production batches (as well as one batch per year) will be monitoring by the analytical or quality control department.

The stability now becomes the formal stability testing of the marketed product.

The first (yearly) report will reassess the temporary expiration date.

Changes in formula or procedure of existing products

When the procedure or formula has been changed for pressing reasons, the change must be filed in a amendment and stability data must be included.

Usually, accelerated data demonstrating compatibility with the previous approved drug product plus the standard commitment to continue the stability study, will suffice.

Since reaction orders are known at this point, extrapolation can be used with more confidence.

Conclusions

Stability testing of drug substances and drug products

<u>begins</u>

as part of drug discovery and synthesis or development-preformulation and

<u>ends only</u>

with the demise of the compound or commercial product.

A glance to ICH

(International Conference Harmonization) guidelines

ICH Stability Guidelines

The ICH Stability Guideline Q1A(R2) defines the stability data package for a new drug substance or drug product that is sufficient for a registration application within the three regions of the EC, Japan, and the United States.

Also adopted by some non-ICH countries including Canada, Australia, Switzerland.

General Principles

The purpose of stability testing is:

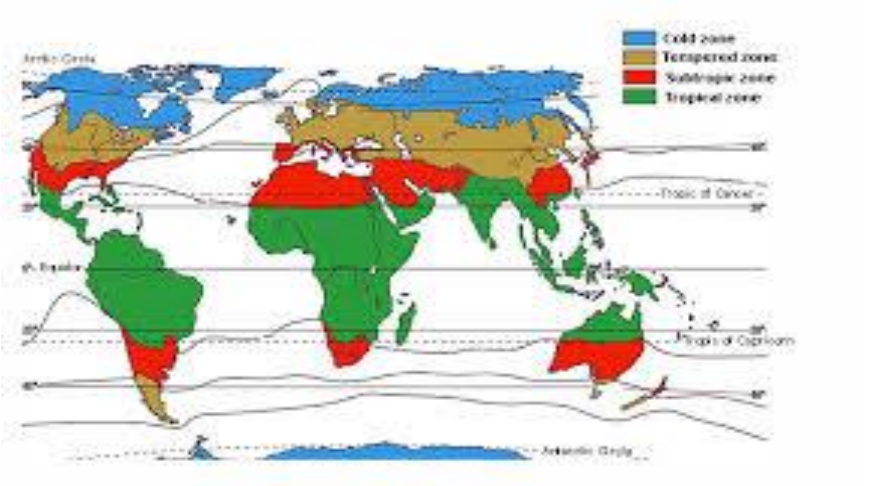
- to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, and
- to establish a re-test period for the drug substance or a shelf life for the drug product and recommended storage conditions.

The choice of test conditions defined in this guideline is based on an analysis of the effects of climatic conditions in the three regions of the EC, Japan and the United States (climatic zones I and II).

ICH Stability Zones

Zone	Type of Climate
Zone I	Temperate zone
Zone II	Mediterranean/subtropical zone
Zone III	Hot dry zone
Zone IV	Hot humid/tropical zone
Zone IVb	ASEAN (Association of Southeast Asian Nations) testing conditions hot/higher humidity

World view of climatic zones



Long Term Testing Conditions

Climatic Zone	Temperature	Humidity	Minimum Duration
Zone I	21ºC ± 2ºC	45% RH ± 5% RH	12 Months
Zone II	25ºC ± 2ºC	60% RH ± 5% RH	12 Months
Zone III	30ºC ± 2ºC	35% RH ± 5% RH	12 Months
Zone IV	30ºC ± 2ºC	65% RH ± 5% RH	12 Months
Zone IVb	30ºC ± 2ºC	75% RH ± 5% RH	12 Months
Refrigerated	5ºC ± 3ºC	No Humidity	12 Months
Frozen	-15ºC ± 5ºC	No Humidity	12 Months

Accelerated and Intermediate Testing Conditions

Climatic Zone	Temperature	Humidity	Minimum Duration
Accelerated Ambient	40ºC ± 2ºC	75% RH ± 5% RH	6 Months
Accelerated Refrigerated	25ºC ± 2ºC	60% RH ± 5% RH	6 Months
Accelerated Frozen	5ºC ± 3ºC	No Humidity	6 Months
Intermediate	30ºC ± 2ºC	65% RH ± 5% RH	6 Months

Drug Product Stability

General

- The design of the formal stability studies for the drug product should be based on knowledge of the behavior and properties of the drug substance and from stability studies on the drug substance and on experience gained from clinical formulation studies.

Photostability Testing

- It should be conducted on at least one primary batch of the drug product (ICH Q1B).

Selection of Batches

- Data from stability studies should be provided on at least three primary batches of the drug product. The primary batches should be of the same formulation and packaged in the same container closure system as proposed for marketing.

Container Closure System

- Stability testing should be conducted on the dosage form packaged in the container closure system proposed for marketing.

Drug Product Stability

Specification

- Specification is a list of tests, reference to analytical procedures, and proposed acceptance criteria, including the concept of different acceptance criteria for release and shelf life specifications (ICH Q6A and Q6B); in addition, specification for degradation products in a drug product (Q3B R2).
- Stability studies should include testing of those attributes of the drug product that are susceptible to change during storage and are likely to influence quality, safety, and/or efficacy.
- The testing should cover the physical, chemical, biological, and microbiological attributes, preservative content (e.g., antioxidant, antimicrobial preservative), and functionality tests (e.g., for a dose delivery system).
- Analytical procedures should be fully validated and stability indicating.

Drug Product Stability

Testing Frequency

- For long term studies, frequency of testing should be sufficient to establish the stability profile of the drug product.

- For products with a proposed shelf life of at least 12 months, the frequency of testing at the long term storage condition should normally be every 3 months over the first year, every 6 months over the second year, and annually thereafter through the proposed shelf life.

- At the accelerated storage condition, a minimum of three time points, including the initial and final time points (e.g., 0, 3, and 6 months), from a 6-month study is recommended

Drug Product Stability

Storage Conditions

- In general, a drug product should be evaluated under storage conditions that test its thermal stability and its sensitivity to moisture or potential for solvent loss.
- The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment, and subsequent use.
- The long term testing should cover a minimum of 12 months' duration on at least three primary batches at the time of submission and should be continued for a period of time sufficient to cover the proposed shelf-life.
- Data from the accelerated storage condition and, if appropriate, from the intermediate storage condition can be used to evaluate the effect of short term excursions outside the label storage conditions (such as might occur during shipping).

Drug Product Stability

General case

Study	Storage condition	Minimum time period covered by data at submission
Long term*	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH	12 months
Intermediate**	30°C ± 2°C/65% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months

**It is up to the applicant to decide whether long term stability studies are performed at 25 ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH.*

***If 30°C ± 2°C/65% RH ± 5% RH is the long-term condition, there is no intermediate condition.*

Drug Product Stability

- If long-term studies are conducted at 25°C ± 2°C/60% RH ± 5% RH and "significant change" occurs at any time during 6 months' testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria.

- The initial application should include a minimum of 6 months' data from a 12-month study at the intermediate storage condition.

- If the long-term data show variability, verification of the proposed retest period or shelf life by statistical analysis can be appropriate.

Drug Product Stability

In general, "significant change" for a drug product is defined as:

1. A 5% change in assay from its initial value; or failure to meet the acceptance criteria for potency when using biological or immunological procedures;
2. Any degradation product's exceeding its acceptance criterion;
3. Failure to meet the acceptance criteria for appearance, physical attributes, and functionality test (e.g., color, phase separation, resuspendibility, caking, hardness, dose delivery per actuation);

   however, some changes in physical attributes (e.g., softening of suppositories, melting of creams) may be expected under accelerated conditions ;

and, as appropriate for the dosage form:

4. Failure to meet the acceptance criterion for pH; or
5. Failure to meet the acceptance criteria for dissolution for 12 dosage units.

Drug Product Stability

Stability Commitment

- When available long term stability data on primary batches do not cover the proposed shelf life granted at the time of approval, a commitment should be made to continue the stability studies post approval in order to firmly establish the shelf life.

- If the submission includes data from stability studies on at least three production batches, a commitment should be made to continue the long term studies through the proposed shelf life and the accelerated studies for 6 months.

Drug Product Stability

Evaluation

- A systematic approach should be adopted in the presentation and evaluation of the stability information, which should include, results from the physical, chemical, biological, and microbiological tests, including particular attributes of the dosage form (for example, dissolution rate for solid oral dosage forms).
- Where the data show so little degradation and so little variability, it is normally unnecessary to go through the formal statistical analysis.
- An approach for analyzing data of a quantitative attribute that is expected to change with time is to determine the time at which the 95 one-sided confidence limit for the mean curve intersects the acceptance criterion.

Drug Product Stability

Statements/Labeling

- A storage statement should be based on the stability evaluation of the drug product.
- Where applicable, specific instruction should be provided, particularly for drug products that cannot tolerate freezing.
- Terms such as “ambient conditions” or “room temperature” should be avoided.
- There should be a direct link between the label storage statement and the demonstrated stability of the drug product.
- An expiration date should be displayed on the container label.

Degradation Products in New Drug Products

- The summary of the degradation products observed during manufacture and/or stability studies should be based on sound scientific appraisal of potential degradation pathways in the new drug product and impurities arising from the interaction with excipients and/or the immediate container closure system. In addition

- Any degradation product observed in stability studies conducted at the recommended storage condition should be identified when present at a level greater than (>) the identification thresholds.

- Degradation products present at a level of not more than (≤) the identification threshold generally would not need to be identified.

- However, analytical procedures should be developed for those degradation products that are suspected to be unusually potent, producing toxic or significant pharmacological effects at levels not more than (≤) the identification threshold.

Thresholds for Degradation Products in New Drug Products

Reporting Thresholds

Maximum Daily Dose [1]	Threshold [2,3]
≤ 1 g	0.1%
> 1 g	0.05%

Identification Thresholds

Maximum Daily Dose [1]	Threshold [2, 3]
< 1 mg	1.0% or 5 µg TDI, whichever is lower
1 mg - 10 mg	0.5% or 20 µg TDI, whichever is lower
>10 mg - 2 g	0.2% or 2 mg TDI, whichever is lower
> 2 g	0.10%

Qualification Thresholds

Maximum Daily Dose[1]	Threshold[2,3]
< 10 mg	1.0% or 50 µg TDI, whichever is lower
10 mg - 100 mg	0.5% or 200 µg TDI, whichever is lower
>100 mg - 2 g	0.2% or 3 mg TDI, whichever is lower
>2 g	0.15%

[1] The amount of drug substance administered per day

[2] Thresholds for degradation products are expressed either as a percentage of the drug substance or as total daily intake (TDI) of the degradation product. Lower thresholds can be appropriate if the degradation product is unusually toxic.

[3] Higher thresholds should be scientifically justified.

Specifications: New Chemical Drug Substances and Products

A specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described.

It establishes the set of criteria to which a new drug substance or new drug product should conform to be considered acceptable for its intended use.

"Conformance to specifications" means that the drug substance and / or drug product, when tested according to the listed analytical procedures, will meet the listed acceptance criteria.

Specifications: New Chemical Drug Substances

Universal Test / Criteria

The following tests and acceptance criteria are considered generally applicable to all new drug substances.

a) Description
b) Identification.
c) Assay
d) Impurities (*organic impurities and residual solvents*)

Specific Tests / Criteria

In addition to the universal tests listed above, the following tests may be considered on a case by case basis for drug substances

a) Physicochemical properties (*pH of an aqueous solution, melting point, and refractive index*)
b) Particle size
c) Polymorphic forms (*including pseudopolymorphs, and amorphous forms. Solid state IR, X-ray powder diffraction, thermal analysis procedures like DSC, TGA and DTA, Raman spectroscopy, optical microscopy, and solid state NMR should be applied*).
d) Tests for chiral new drug substances (*Where a new drug substance is predominantly one enantiomer, the opposite enantiomer is excluded from the qualification and identification thresholds*)
e) Water content
f) Inorganic impurities
g) Microbial limits

Specifications: New Chemical Drug Products

The following tests and acceptance criteria are considered generally applicable to all new drug products:

a) Description

b) Identification

c) Assay

d) Impurities (organic and inorganic impurities, as degradation products, and residual solvents)

Specific Tests / Criteria

Additional tests and acceptance criteria generally should be included for particular new drug products (*solid oral drug products, liquid oral drug products, and parenterals*).

Solid oral drug products

The following tests are applicable to tablets (coated and uncoated) and hard capsules. One or more of these tests may also be applicable to soft capsules and granules.

a) Dissolution

b) Disintegration

c) Hardness/friability

d) Uniformity of dosage units

e) Water content

f) Microbial limits

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Specifications: New Chemical Drug Products

Oral liquid drug products

One or more of the following specific tests will normally be applicable to oral liquids and to powders intended for reconstitution as oral liquids.

a) Uniformity of dosage units

b) pH

c) Microbial limits

d) Antimicrobial preservative content (*for oral liquids needing an antimicrobial preservative*)

e) Antioxidant preservative content

f) Extractables (*where data demonstrate the need to test extractables from the container/closure system components, e.g., rubber stopper, cap liner, plastic bottle, etc.*)

g) Alcohol content

h) Dissolution (*for oral suspensions and dry powder products for resuspension*)

i) Particle size distribution (for suspensions)

j) Redispersibility

k) Rheological properties

l) Reconstitution time

m) Water content (*for oral products requiring reconstitution*)

Specifications: New Chemical Drug Products

Parenteral Drug Products

The following tests may be applicable to parenteral drug products.

a) Uniformity of dosage units.

b) pH

c) Sterility

d) Endotoxins

e) Particulate matter

f) Water content (*for non-aqueous parenterals, and for products for reconstitution*)

g) Antimicrobial preservative content (*for multidose parenteral products*)

h) Antioxidant preservative

i) Extractables (*for parenteral products packaged in non-glass systems or in glass containers with elastomeric closures*)

j) Functionality testing of delivery systems (*parenteral formulations packaged in pre-filled syringes, autoinjector cartridges*)

k) Osmolarity (*when the tonicity of a product is declared in its labeling*)

l) Particle size distribution (*for injectable suspensions*)

m) Redispersibility *(for injectable suspensions which settle on storage, produce sediment)*

n) Reconstitution time (*for all parenteral products which require reconstitution*).

Validation of Analytical Procedures

The objective of the analytical procedure should be clearly understood since this will govern the validation characteristics which need to be evaluated.

Typical validation characteristics which should be considered are listed below:

- Accuracy
- Precision
  - Repeatability
  - Intermediate Precision
- Specificity
- Detection Limit
- Quantitation Limit
- Linearity
- Range.

Validation of Analytical Procedures

ANALYTICAL PROCEDURE

The analytical procedure refers to the way of performing the analysis and should describe in detail the steps necessary to perform each analytical test.

This may include but is not limited to: the sample, the reference standard and the reagents preparations, use of the apparatus, generation of the calibration curve, use of the formulae for the calculation, etc.

SPECIFICITY

Specificity is the ability to assess unequivocally the analyte in the presence of components which may be expected to be present, typically including impurities, degradants, matrix, etc.

This definition has the following implications: identification, purity, assay (content or potency).

Validation of Analytical Procedures

ACCURACY

- The accuracy of an analytical procedure expresses the closeness of agreement between the value which is accepted either as a conventional true value or an accepted reference value and the value found.

PRECISION

- The precision of an analytical procedure expresses the closeness of agreement between a series of measurements obtained from multiple sampling of the same homogeneous sample.
- Precision should be investigated using homogeneous, authentic samples. However, if it is not possible to obtain a homogeneous sample it may be investigated using artificially prepared samples or a sample solution.
- The precision of an analytical procedure is usually expressed as the variance, standard deviation or coefficient of variation of a series of measurements.

Validation of Analytical Procedures

Precision may be considered at three levels: repeatability, intermediate precision and reproducibility.

Repeatability

- Repeatability expresses the precision under the same operating conditions over a short interval of time. Repeatability is also termed intra-assay precision .

Intermediate precision

- Intermediate precision expresses within-laboratories variations: different days, different analysts, different equipment, etc.

Reproducibility

- Reproducibility expresses the precision between laboratories (collaborative studies, usually applied to standardization of methodology).

Validation of Analytical Procedures

DETECTION LIMIT

- The detection limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be detected but not necessarily quantitated as an exact value.

QUANTITATION LIMIT

- The quantitation limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be quantitatively determined with suitable precision and accuracy.

- The quantitation limit is a parameter of quantitative assays for low levels of compounds in sample matrices, and is used particularly for the determination of impurities and/or degradation products.

Validation of Analytical Procedures

LINEARITY

- The linearity of an analytical procedure is its ability (within a given range) to obtain test results which are directly proportional to the concentration (amount) of analyte in the sample.

RANGE

- The range of an analytical procedure is the interval between the upper and lower concentration (amounts) of analyte in the sample for which it has been demonstrated that the analytical procedure has a suitable level of precision, accuracy and linearity.

ROBUSTNESS

- The robustness of an analytical procedure is a measure of its capacity to remain unaffected by small, but deliberate variations in method parameters and provides an indication of its reliability during normal usage.