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S T A B I L I T Y T E S T I N G I N I N D U S T R Y

F O R W O R L D W I D E M A R K E T I N G

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Abstract

Today Stability Tests are an integral part of Industry's Quality Assurance Programme. The stability predictions derived from the results of the Tests represent a comprehensive assessment of quality, which applies to all batches and includes organoleptic, physicochemical, chemical and where applicable, microbiological criteria.

The aim is to describe, from Industry's point of view, what outlay is necessary for Stability Testing for worldwide marketing and what degree of confidence lies behind the stability predictions.

Along the way from a new drug substance to routine production, 3 phases in Stability Testing can be distinguished:

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- Preliminary and Stress experiments
- Long term testing
- Follow-up studies

Each phase has its own specific aim. The outlay and scope devoted to each phase must be appropriate to the particular problem. It is shown, which storage conditions are necessary, especially for the worldwide introduction of a drug product, the testing criteria, testing methods, number of batches and samples, duration of study and sequence. Finally the evaluation with the derivation of periods of stability is described.

Introduction

The transition to industrial production led to the necessity of undertaking stability tests, which can ensure that the patient obtains medicines, the full activity of which is guaranteed until the end of the shelf life.

With the increasing industrialisation of the drugs market and the introduction into countries of different climatic zones, the expenditure and complexity of stability testing has markedly increased.

Thus especially in the drugs industry, stability testing has, over the years, developed into an inter-disciplinary science, which has long since gone beyond purely analytical confines, and which today represents a symbiosis of analysis, pharmaceutical technology, biochemistry and physical chemistry.

Stability Testing pursues two particular aims:

- Selection of the optimal formulation during pharmaceutical-technological development

- Derivation of periods of stability, which ensure that the product retains its full activity up to the end of its shelf life.

These investigations, required because of the manufacturer's responsibility for the quality of his drug product, must be orientated towards therapeutic, pharmaceutical-technological and analytical advances.

The shelf life periods derived from the results of the stability tests relate to the preparation, all batches of it and include organoleptic, physicochemical, chemical and, where applicable, microbiological criteria. The test results also form the basis for registration or licensing documents.

The aim of this paper is to show what industry contributes to drug safety within the framework of stability testing and to describe its underlying principles.

Structure

Preliminary and Stress experiments

The preliminary and stress experiments cover the following stages in development:

- Determination of the stability profile for the drug
- Design of the formulation
- First laboratory scale production

The purpose of the preliminary and stress tests is to,

- Clarify those factors which affect the stability of the drug,
- Identify the weak points of a formulation,
- Validate investigative methods,
- Elaborate packaging proposals,
- Derive provisional shelf lives.

The results needed are provided from the studies with the extreme stress samples.

Long term testing

This phase of development covers the transition from laboratory to full scale production.

The long term tests serve to:

- Confirm the results of the preliminary and stress tests,
- Derive worldwide shelf life periods.

For a whole range of dosage forms they also form the basis of stability studies, since with certain drug forms, only limited stress experiments can be undertaken.

The long term tests thus provide the actual core of the stability investigations.

The results form the basis for:

- Mandatory statements on stability
- Registration of Licensing documents.

Follow-up studies

The purpose of the follow-up studies is to:

- Monitor routine production
- Check the validity of earlier stability predictions and to confirm them statistically.

By the systematic execution of stability testing in these three phases, it should be possible to

- achieve a constant widening of the information on the stability of a preparation,
- derive reliable stability data at the earliest possible stage.

If one looks at the overall expenditure and effort involved in developing a drug, then it is clear that certain differences exist in expenditure per time unit.

Thus preliminary and stress experiments reduce the effort involved in long term testing. In addition they enable a reliable prediction of stability to be made much quicker.

Requirements

Before stability testing can actually be started, a number of points must be clarified.

Storage conditions

The correct choice of storage conditions is extremely important. That applies both to preliminary and stress tests as well as to the long term testing and the follow-up studies.

The storage conditions must be derived very carefully; it must be clear which conditions one wishes to simulate.

Storage conditions for Long term testing:

For worldwide stability tests, the earth is divided into four climatic zones (3), into which the individual countries are assigned.

The zones are characterised as follows:

I	Temperate climate
II	Mediterranean-like and subtropical climate
III	Hot, dry climate, dry regions
IV	Hot, humid climate, Tropics

Temperature and humidity determine climate and hence also the particular storage condition derived.

Both factors quite decisively influence the stability of the drug and can cause organoleptic, physicochemical, chemical and microbiological alterations.

The Arrhenius equation provides the functional correlation for the influence of temperature on chemical stability. Thus a linear relationship exists

between the log of the rate constant k and the reciprocal of the absolute temperature,

$$\log k = f\left(\frac{1}{T}\right)$$

The resulting consequences for storage temperature are shown in Fig. 1 (4)

As can be seen from this example, the shelf life is reduced from 5 to 4 years, when the storage temperature is increased from 25°C to 27°C.

The storage condition must therefore not represent an unrealistic stress, otherwise false shelf life periods will be deduced.

The laws of reaction kinetics must also be considered in the derivation of storage temperature, where, instead of the average temperature, the kinetic average temperature must be calculated (5 - 7). If, for example, a sample is stored for one month at 20°C and 1 month at 40°C, the arithmetic mean is given as 30°C. The kinetic average temperature is however, 34,2°C.

The second factor determining a storage condition, in addition to temperature, is the relative humidity. Here the Clausius-Clapeyron equation shows the connection between the vapour pressure of water and the absolute temperature

$$\ln P = -\frac{\Delta H_V}{R} \cdot \frac{1}{T} + \text{constant}$$

ΔH_V is here the molar heat of evaporation.

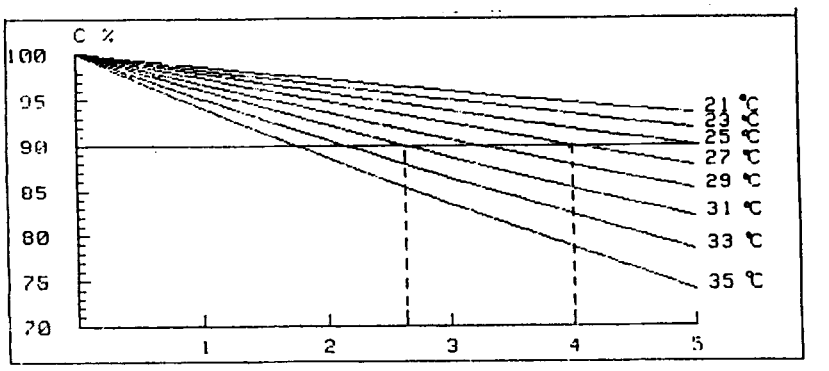

Figure 1: Potency of active ingredient as a function of the temperature. Base value: 25°C, 5 years, potency 90%

At a given pressure, the partial pressure of water vapour in moist air can be maximally equal to the partial pressure of water at the same temperature, the saturation pressure, P_s. Also important is the

$$\text{relative humidity } \varphi = \frac{P_D}{P_s} \cdot 100$$

P_D is the appropriate partial pressure.

If the partial pressure P_D remains constant and the temperatur changes, then the relative humidity will also alter.
See the example given in Table 1.

To determine storage conditions, one turns to climatic data which are available for all countries. The figures were however measured in the open air and must therefore be corrected in the light of the following points:

- Drugs are stored in closed and sometimes air-conditioned rooms. Therefore one takes 19°C for all

Table 1: Change in relative humidity with temperature at a constant pressure of 6.1 mbar.

Temp. [°C]	0	5	10	15	20	25	30	35	40	45	50
rel. humidity [%]	100	70	50	36	26	19	14	11	8	6,4	4,9

temperature values < 19°C and calculates the resultant mean value for each month.
Calculation of the relative humidity for the determined temperature

In Table 2 the measured and calculated climatic data for Los Angeles are given as an example of a city in Climatic Zone II (8)

Next, 12 typical cities are chosen from each climatic zone and the climatic data treated as the example of Los Angeles (9 - 11).

The resultant mean values are summarised in Table 3.

It is now interesting to compare the calculated average values with climatic data that were measured in storage rooms (15, 16). At the same time, temperature and relative humidity were calculated for those cities in which the storage rooms are situated, from data measured in the open. (see Table 4)

Table 2

Month	Jan.		Feb.		March		April		May		June	
	7.00	14.00	7.00	14.00	7.00	14.00	7.00	14.00	7.00	14.00	7.00	14.00
Measured temp. (°C)	8.1	18.3	9	18.9	10.1	20.3	11.8	21.4	13.3	23.1	14.9	25.1
Measured r.H. (%)	63	50	71	52	74	52	78	54	81	55	85	56
Partial press. (mbar)	7	10.5	8	11.5	9	12.5	11	13.5	12.5	15.5	14.5	17.5
Temp. < 19 °C taken as 19 °C	19	19	19	19	19	20.3	19	21.4	19	23.1	19	25.1
Average temp./Mon. (°C)	19		19		19.7		20.2		21.1		22.1	
r.H. calc. for each month (%)	40		44		47		54		56		61	
Month	July		Aug.		Sept.		Oct.		Nov.		Dec.	
	7.00	14.00	7.00	14.00	7.00	14.00	7.00	14.00	7.00	14.00	7.00	14.00
Measured temp. (°C)	17	28.5	17.7	28.5	16.3	28	14.1	25.2	11.2	22.9	9.3	19.7
Measured r.H. (%)	84	53	84	55	78	54	76	56	61	49	62	50
Partial press. (mbar)	16.5	20.5	17	21.5	14.5	20.5	12	18	8	13.5	7.5	11.5
Temp. < 19 °C taken as 19 °C	19	28.5	19	28.5	19	28	19	25.2	19	22.9	19	19.7
Average temp./Mon. (°C)	23.8		23.8		23.5		22.1		21		19.4	
r.H. calc. for each month (%)	60		66		60		56		43		42	

Table 3: Data for the various Climatic Zones, derived from values that were measured in the open

$T_{meas.}$ = measured temp.,
$T_{cal.}$ = calculated temp.
T_K = kinetic average temp.,
P_D = partial pressure

Climatic Zone	Average values				
	$T_{meas.}$ [°C]	$T_{cal.}$ [°C]	T_K [°C]	P_D [mbar]	r.H. [%]
I	10,7	19,7	19,7	10,0	43,9
II	18,8	22,3	22,8	14,2	52,9
III	24,9	26,9	28,1	11,1	31,5
IV	27,0	27,0	27,5	27,9	78

Table 4: Climatic values measured in storage rooms and calculated for the respective city. In each case, mean values were calculated.

Climatic zone	climatic values measured in storage rooms		climatic values calculated	
	T [°C]	r.H. [%]	T [°C]	r.H. [%]
I	18,7	45,3	19,6	46,0
II	21,1	58,0	21,1	56,2
III	26,0	53,5	28,4	35,3
IV	28,4	70,2	26,4	75,1

There is a good agreement.

The storage conditions for the four climatic zones are now derived from the calculated climatic data. The following criteria are taken into consideration:

- all individual values of the respective 12 cities,
- data measured in storage rooms,
- safety factor added for temperature and relative humidity

The data are shown in Table 5 (12 - 14).

The storage conditions may vary symmetrically within the following limits (17, 18)

Temperature $\pm$ 2°C Relative Humidity $\pm$ 5 %

Storage conditions should encompass those climatic influences to which the drug is exposed in the respective climatic zones. That means both seasonal and daily variations.

The annual course of temperature is thus firstly taken into account in that one differentiates between average months, hot and very hot months. The resultant kinetic average temperature is calculated at the same time.

Secondly, the daily variations in temperature in the hot and the very hot months are considered, with 8 hours for the night, and 6 hours each for morning and afternoon and the four hottest hours. See Tables 6 and 7.

Table 5: Climatic values for the four climatic zones and the derived storage conditions.

Climatic Zone	Calculated			Derived storage condition		
	T[°C]	r.H. [%]	P [mbar]	T [°C]	r.H. [%]	P [mbar]
I	19,7	43,9	10,0	21	45	11,2
II	22,3	52,9	14,2	25	60	19
III	26,9	31,5	11,1	31	40	18
IV	27,0	78	27,9	31	70	31,5

The storage conditions derived from the measured climatic values fulfill the following criteria:

- They conform to the official definitions of room temperature
  Ph.Eur. II 15 - 25°C = 21,1°C as TK ≙ Climatic Zone I
  USP XXI 15 - 30°C = 25,1°C as TK ≙ Climatic Zone II
  (19)

- Seasonal and daily temperature variations are taken into account.

- They are above the values measured in storage rooms
- They lie above the calculated climatic values
- They are higher than the individual values of the respective 12 cities.

Realistic and also reliable shelf life periods can be derived from results of studies with samples stored under these conditions, corresponding to the added safety factor applied.

Table 6: Simplified annual course of temperature and the resulting kinetic average temperatures.

Climatic zone	Simplified annual course of temperature in months (M)	Kinetic average temperature, TK (°C)
I	8 M 19°C, 3 M 23°C, 1 M 25°C	20,8
II	6 M 21°C, 4 M 26°C, 2 M 30°C	25,1
III	4 M 25°C, 4 M 30°C, 4 M 34°C	30,3
IV	4 M 27°C, 4 M 29°C, 4 M 31°C	29,1

Table 7: Daily temperature variations in the hot and hottest months with the permitted maximal temperatures for 4 hours in each case and the resultant kinetic average temperature.

Climatic zone	Temp./time	Daily temp. course 8 h	6 h	4 h	6 h	TK
I	23°C/3 Monate	20°C	22°C	26°C	24°C	22,7°C
I	25°C/1 Monat	20°C	24°C	31°C	26°C	25,1°C
II	26°C/4 Monate	21°C	25°C	31°C	27°C	26,1°C
II	30°C/2 Monate	24°C	28°C	36°C	32°C	29,9°C
III	30°C/4 Monate	24°C	28°C	36°C	32°C	29,9°C
III	34°C/4 Monate	25°C	32°C	42°C	36°C	34,2°C
IV	29°C/4 Monate	26°C	28°C	32°C	30°C	28,7°C
IV	31°C/4 Monate	26°C	28°C	35°C	32°C	30,1°C

Storage conditions for stress experiments:

By stress storage the samples should be subjected to extreme conditions. Therefore the storage parameters differ fundamentally from those for the climatic zones.

Nevertheless it must be possible to draw conclusions from these tests for long term testing and the various climatic zones.

If for example, samples are stored at 37°C/75 % r.H. - a condition that one frequently finds quoted in the literature-, then one can compare different formulations or packaging materials relative to one another and select the best, but no absolute statement about stability can be made.

Thus the adsorption behaviour of placebo tablets (lactose 82,3 mg, corn starch 37,5 mg, magnesium stearate 0,5 mg) was investigated, where samples were stored in each case up to the attainment of equilibrium (13). See Table 8

In this example, the adsorption decreases with constant relative humidity and increasing temperature, but the equilibrium is reached more slowly (20).

A second example shows the sorption characteristics of another tablet at 75 % r.H. and increasing temperature (21).

Adsorption curves 75 % r.H.

The conclusion to be drawn from these results is that if one wishes to make deductions concerning behaviour

Table 8: Increase in weight of tablets with various storage conditions.

Storage condition (°C) (r.H)	Partial press. PD (mbar)	Water content of the air (g/m^3)	Increase in weight (%)	Time for 50 % (h)
21 / 60	14,9	11,1	2,7	80 min
26 / 60	20,2	14,6	2,3	50 min
31 / 60	26,9	19,2	2,1	45 min
41 / 84	65,3	45,1	2,6	20 min

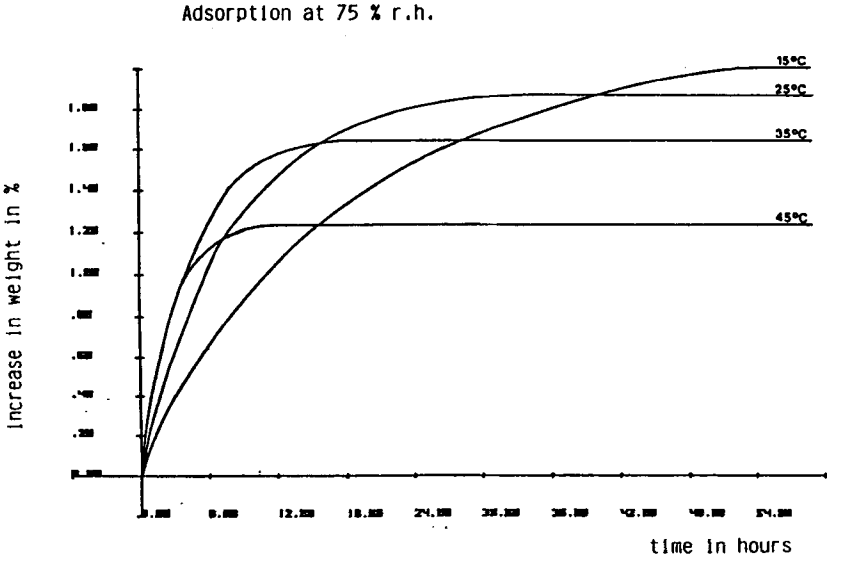

Fig. 2: The dependence of adsorption curves on storage temperature.

at lower temperatures, then solid dosage forms can only be stored at high temperatures in packaging materials impermeable to moisture.

With stress storage, one differentiates between the testing for chemical stability in moisture-tight containers at temperatures between 81°C und 41°C (2), depending on the dosage form, and testing for organoleptic and physicochemical changes.

Conditions are adapted to the various dosage forms and the test criteria.

These include:

Liquid forms:	- 10°C
Semi-solid forms:	- 10°C Alternating temperature between 4°C and 41°C
Solid dosage forms:	Open storage of the sample until attainment of equilibrium at 21°C/45 %, 25°C/60 %, 31°C/40 %, 31°C/70 %

Storage conditions for follow-up studies:

To monitor routine production, storage is carried out at 41°C or 31°C/70 %.

To test retained reference samples after expiry of the shelf life, storage at room temperature is of advantage, though an accompanying recording of temperature and relative humidity is necessary.

Test criteria:

In stability testing, the product must be assessed in its entirety, that means that organoleptic, physicochemical, chemical and where applicable, microbiological test criteria are all to be considered.

In concrete terms, this means selecting those criteria of a preparation for investigation which:

- can undergo an alteration during storage
- are of particular relevance for the quality, effectiveness or acceptance.

Often the final selection of the test criteria is not made until the results of the stress experiments are available.

In every case the test parameters must be scrupulously chosen, since this can markedly influence both the expenditure on stability tests and also the stability prediction.

A typical example is the criteria of dissolution rate with solid dosage forms. If the product in question contains a problem drug corresponding to the definition of the Federal Register of the FDA

- limited solubility of the active ingredient
  < 5 mg/5 ml $\hat{=}$ Cs $< 0,5$ %
- low rate of dissolution
  $V_d < 50$ %/30 min in 900 ml
  (V_d = rate of dissolution)

and other criteria

- applied dosage form is well over the amount that will dissolve in 100 ml gastric juice
  Dose >> solubility in 100 ml
- occurrence of modifications to the active ingredient (also complexes) which produce slower dissolution rate,

then dissolution testing is indispensable. With easily soluble drugs it is unjustified, since the determination of disintegration time provides the decisive statement.

Investigative methods and techniques

The predictive value of the results of stability testing depends very largely on the test methods used. They must ensure that any changes arising in any of the test criteria are clearly and unequivocally detected.

The methods for determining content must be specific and validated, i.e. the following points are to be observed:

- Specificity
- Linearity
- Sensitivity
- Accuracy / recovery rate
- Precision
- Ruggedness
- Critical parameters
- Quantitatively measurable limit of detection

The physical and physicochemical techniques should be quantitative wherever possible.

Objective instead of verbal descriptions should be used as far as possible in the organoleptic assessment of changes.

Generally several measurements are obtained in the determination of physicochemical criteria, which can be evaluated with the help of statistics.

Tolerances

If one has established the relevant testing points and chosen suitable methods, then one can evaluate the preparation with the results obtained.

The basis for its quality and thus also for decisions is provided by the tolerances (21). For evaluating a drug preparation by the quality control immediately after manufacture (finished product/fresh goods), manufacturing and analytical tolerances have to be taken into account.

Similarly, tolerances must be set for changes that arise during stability testing as maximum acceptable alterations, which may not be exceeded before the end of the shelf life. For many test criteria, that is by no means simple. But the effectiveness of a drug must not be impaired by the changes.

Hence the determination and establishment of tolerances is a decisive step in assessing the quality of a drug product.

Tolerances can be determined and evaluated from the following data:

- Results from the literature
- Results from formula variants made during the optimisation process
- Results from validation
- Results from analogous or parallel formulations
- Results of biochemical and toxicological investigations
- Legal requirements
- Results of preliminary and stress experiments.

In the actual case, one proceeds in a stepwise manner:

The first stage is to determine the predictive value of the investigative techniques and methods. With the statistical data so obtained, it is possible to ascertain whether significant changes have occurred compared to the initial or theoretical value.

If the change is acceptable, then the limiting value derived from the experimental error serves as an internal warning limit.

The next step is to discover all the possible changes that can arise during storage and decide what tolerance limits must be applied to them.

It is particularly difficult to establish limits in relation to organoleptic and physicochemical testing points.

Here there are no laws corresponding to the reaction kinetics for the active ingredient. An important basis for determining and evaluating changes in physico-chemical properties is given by the molecular-galenical considerations of Hüttenrauch (22 - 32).

Table 9: Limits of significance to detect changes and limits for maximum acceptable changes for tablets

Testing point	Limit of significance as internal warning to detect a change	Tolerance limit for max. acceptable changes
Appearance	2 grades	e.g. 3 grades
Hardness	± 3,5 % = 2,1 N	20 N
Disintegration Time	± 23 %	15 min
Rate of dissolution	± 10 %	75 % / 45 min or 56 % / 45 min
Average weight	± 2 %	-
Degradation of active ingred.	0,5 - 1 %	10 %
Content of active ingred.	3 %	90 % content relative to the theoretical value

Table 9 shows the significance and tolerance limits for maximal acceptable changes for tablets as an example (33).

If degradation does occur, then the question of the toxicity of the degradation products must also be addressed.

Batch selection, Sampling

The period of stability for a drug preparation is derived from the results of investigations with just a

few batches. Hence the batches must be carefully selected.

One must distinguish between experimental batches and representative batches.

- Experimental batches: This is often the first lot. It is stored to enable a new formulation or a new step in the process to be evaluated. In broad terms, it involves assessing the relative change compared to an initial value.

- Representative batches: Such a batch is representative of the respective stage of development, it is only stored once the particular development phase is concluded and manufacture has been mastered, i.e. the process has been validated.

  That applies to laboratory, pilot-plant and production batches, to manufacture and packaging.

  The representative batch must correspond to the current specifications with regard to the various test points.

  It should however be pointed out here that in many cases, there is no significant difference between experimental and representative batches.

Next the sample stored for stability testing must be representative of the respective batch. The analytical sample must in each case be taken and treated in such a manner that the result is representative of the batch at the time of analysis.

Execution

The execution of the stability test must be very carefully thought through. The effort needed is determined for each particular problem and should not proceed on purely formalistic grounds.

Establishment of a Requirement Profile

As the first step in carrying out a stability test, the problem must first be set out clearly. The following questions should be addressed:

- Is it proposed to introduce the preparation into a single country, a single climatic zone or worldwide?
- Is it a new drug in a new preparation, a parallel development or a formula variant?
- What packaging materials might be used?
- With what priority is the project to be pursued?
- Is there already a provisional registration-, licensing- or introduction date?

The next stage is to list all factors which can influence the stability of the formulation or the preparation, and which must be covered by the stability prediction.

One can divide these influencing factors as follows:

- Factors which exert their effects from manufacture up to the moment of use.

Depending on the preparation, this may include statements on the effects of duration of storage, sensitivity to air, light, temperature and moisture.

- Factors which exert their effects during use.

After the requirement profile has been established, it is examined to see how far the individual factors can be covered by results already to hand. Then the necessary investigations can be determined.

Number of batches

The number of batches required depends quite decisively on the particular problem. If one is dealing with a new preparation with a new active ingredient, then the entire stability testing programme should consist of 3 batches of differing size.

If it is a parallel development or a formula variant, then 1 to 2 batches suffice.

If a technical change to the manufacturing technique or a change in a formulation has to be evaluated, then one batch compared to the old formulation is necessary.

Primary packaging material

Basically the primary packaging material intended for the introduction should be used in the stability tests. However the dosage form plays a part here.

With liquid and semi-solid dosage forms, where there is a danger of an interaction between contents and

container, in each case tests must be undertaken in the final primary packaging material.

Nevertheless, with solid forms, in many cases the results of stress tests on the chemical and physico-chemical behaviour and general packaging tests can be used to determine whether the respective packaging material is suitable or not, so that the decision can be taken by analogy.

Duration of study and sequence

The duration of the investigation stretches at least over the entire shelf life. The basis for the sequence of testing forms a fixed framework, with 0, 3, 6, 12, 24, 36, 60 months, which can if necessary be adapted to suit the particular problem.

If, for example, changes occur after 24 months which approach the tolerance limit, then would choose 30 months as the next date for testing to ascertain whether 24 months shelf life is safe.

The aim must be to reduce the number of investigations as far as possible. To this end, knowledge generally obtained is increasing applied to the individual formulations. Efforts should be directed at only investigating those samples where a significant change is likely.

Documentation

The documentation must ensure that every analytical result even the weighing out, can be traced.

Evaluation

The purpose of stability testing is to derive shelf life periods for the preparation. Therefore the test results have to be evaluated accordingly.

However, first of all it must be clearly understood what one means by stability, to what extent changes can be tolerated.

Definition of Stability

According to the APV Guidelines (1), stability can be defined as follows:

Stability means the maintenance of the quality defined in the specifications of the drug product up till the end of the manufacturer's stated shelf life.

The quality of the drug product is determined by the content of active ingredient and the purity, the organoleptic, physicochemical and microbiological properties.

The content of active ingredient of a drug, unless specified by other regulations (eg Pharmacopoeia, EEC-Guidelines) should not fall below 90 % of the declared value before the end of its shelf life.

Degradation products should be identified wherever possible and limited. It must be ensured that degradation products do not lead to any increase in toxicity of the drug concerned.

The quality in respect of the organoleptic, physicochemical and microbiological properties of the drug is considered assured if,

- the test results correspond to the specifications
- the drug can be used as intended
- any changes that arise are not so pronounced that user acceptance is impaired.

This once again illustrates the importance of the specifications.

Derivation of periods of stability

The first question here is how soon shelf lives can be derived.

- If stress experiments are undertaken parallel to long term tests, then reliable shelf life data can be derived after 6 months.

- If the samples are stored under different climatic conditions for a worldwide introduction, then this is possible after 12 months.

- If the samples are merely stored at 21°C/45 % r.H., then this is possible after 24 months at the earliest.

What test results can one draw on to derive shelf life periods?

The basis for a stability prediction is provided by the results of the stress tests and the batches whose composition corresponds to that intended for introduction.

In addition, one can also use the results from formula variants from the development of parallel or analogous

formulations. By this means it will be possible to determine the range of a formula straightaway, and without special effort validate the stability prediction.

To evaluate suitable primary packaging materials one can also use the results of general experiments with the dosage form or the packaging material.

The shelf life relates to the preparation as a whole and must therefore take into account organoleptic, physicochemical, chemical and where applicable, microbiological criteria.

Reaction kinetics and statistics are methods available to derive shelf lives from the results of the stability tests.

The values of content for the various climatic zones are estimated with the help of reaction kinetics from the data of the stress and long term tests. Taking into account a range of criteria (2), the reaction kinetics is a very elegant technique for which there is no alternative.

Statistics are used to compare batches with the help of variance analysis, in regression calculations, to detect significant changes.

An example will show how the process works in detail.

First of all one tests whether it is possible, using reaction kinetics, to predict the values for content for the various climatic zones from the analytical data.

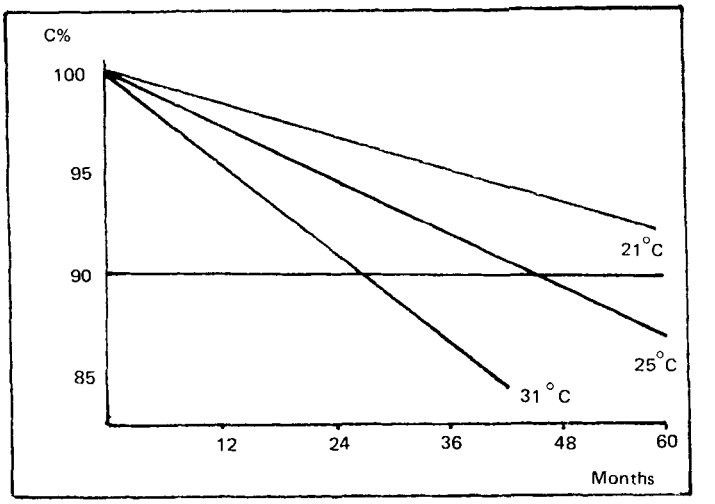

Fig. 3: Content values calculated by reaction kinetics for 21°C, 25°C and 31°C without confidence limits.

If this is the case, see Fig. 3 (34), then one can read directly off the graph when the 90 % content limit is reached at the various storage temperature (corresponding to the climatic zones).

The resulting shelf life periods relate only to the content of active ingredient.

Therefore additional points have to be clarified:

- Have statistically significant changes occurred compared to the initial value?
- Has the limit for maximal acceptable changes already been reached?
- Will the limit have been reached earlier than the shelf life as indicated by the active ingredient?

Stability Certificate

The stability predictions for a preparation or for a formula variant are summarised in a Stability Certificate.

This contains details of the shelf life for the various climatic zones, where appropriate, a list of suitable packaging materials, if necessary, storage directions. In addition, all the data from which the predictions were derived is set out. Finally the results are commentated upon in terms of organoleptic, physico-chemical, chemical and microbiological properties.

It must be made absolutely clear how the shelf lives were derived and confirmed, by which criteria they are limited and whether they could be extended once further results become available.

If the documents are to be passed on externally, in addition:

- a short description is given of the general conception and organisation of the Stability Test,
- a copy is included of the Stability Test Protocol, together with the results used,
- the reaction kinetics calculation is documented.

Conclusions

The reliability of the stability prediction depends, in the first instance, on the basic conception of the

Stability Test and its organisation. Other important factors are sound test criteria, meaningful test methods and the use of reaction kinetics and statistics.

The Stability Certificate with the summarising report, is drawn up either for an internal decision or for registration or licensing application to the authorities.

During the course of stability testing, the stability prediction becomes increasingly firm. Whereas at the start, merely a stability prognosis is made, by the end there are proven shelf lives.

How quickly and confidently a prediction can be made depends on the structure and scope of the Stability Test.

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