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Drug Development and Industrial Pharmacy

ISSN: 0363-9045 (Print) 1520-5762 (Online) Journal homepage: http://www.tandfonline.com/loi/iddi20

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To cite this article: Brahmaiah Kommanaboyina & C. T. Rhodes (1999) Trends in Stability Testing, with Emphasis on Stability During Distribution and Storage, Drug Development and Industrial Pharmacy, 25:7, 857-868, DOI: 10.1081/DDC-100102246

To link to this article: http://dx.doi.org/10.1081/DDC-100102246

Published online: 06 Oct 1999.

Drug Development and Industrial Pharmacy, 25(7), 857–868 (1999)

Trends in Stability Testing, with Emphasis on Stability During Distribution and Storage

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ABSTRACT

This paper reviews contemporary trends in the stability testing of pharmaceutical products. In particular, it considers the progress toward globalization and harmonization and indicates stability problems, which probably will be the focus of attention for pharmaceutical scientists and regulators in the near future. Attention is specifically directed to monitoring stability in the channels of distribution.

INTRODUCTION

Within the past 25 years or so, the stability testing of pharmaceutical products has advanced dramatically from a somewhat haphazard exercise that showed dramatic variations in quality, both within and between various jurisdictions, to an operation based on sound scientific principles that shows a significant degree of commonality in many parts of the world.

Although pharmaceutical scientists and regulators have known for many years that all drug delivery systems—to a varying degree—have a propensity to degrade and thus show a lower level of ''fitness for use,'' it was only in the 1970s that standardized approaches for the reliable quantification of the stability of pharmaceutical products began to emerge.

The stability of pharmaceutical products is a broad area that encompasses many potential routes of degradation. Any change that occurs in a pharmaceutical product, subsequent to its preparation, that adversely affects any attribute of the quality of the product in terms of its fitness for use by a patient is, potentially at least, a matter of concern to pharmaceutical scientists and regulators involved in stability testing.

It is conventional and convenient to classify degradation of pharmaceutical products as being chemical, physical, or biological. However, in many instances these distinctions are not complete. For example, oxidation in a condom (chemical) results in a loss of tensile strength (physical). Also, for many drugs or devices more than one mode of degradation may be possible (1).

In general, we may classify the adverse effects of the

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instability of a pharmaceutical product as modifying efficacy, safety, or ease of use or patient acceptability. In terms of efficacy, the most obvious effect is loss of potency of the drug. Indeed, for many stability studies loss of potency is the key factor in the determination of the shelf life of the product. Usually, we regard 90% of label claim as being the lowest acceptable value of potency. Thus, for many pharmaceutical products an estimation of the time that will elapse (when the product is stored under specified conditions) before the potency is less than 90% of label claim will be central to our stability studies.

Important though loss of potency can be, there is now an increasing recognition that, for some pharmaceutical products, other effects of instability may be of equal or of greater importance than loss of potency. For example, if a degradation product is toxic, it may be that the accumulation of the toxic degradation product is of more critical importance than loss of the active ingredient. Although such occurrences are presently probably relatively rare, the increasing use of protein drugs, for which small changes in structure can have a profound impact on immunogenicity, may result in this situation becoming more likely and therefore deserving of more attention.

In considering the stability of pharmaceutical products, it is essential to consider the totality of the product—drug, excipients, pack, and label. All of these elements can play an important role in the fitness for use of the drug delivery system. For example, if migration of a plasticizer from the plastic bottle into a label causes the ink to become blurred so that the legibility of the information on the label is impaired, this is a matter of concern.

A major factor in the improvement of pharmaceutical stability testing has been the development of analytical methods that are suitable for use in a stability-indicating assay. In particular, the availability of high-performance liquid chromatography (HPLC) has been a real boon to stability testing. It is noteworthy that our definition of a stability-indicating assay has evolved from a method that would allow quantification of a drug in the presence of its degradation products and excipients to a method that allows quantification not only of the drug, but also of major degradation products.

In addition to technical achievements, such as the emergence of HPLC for use in stability-indicating assays, organizational and regulatory developments have also been of great significance in stability testing. During recent years, the substantial number of corporate takeovers and mergers has increased the number of pharmaceutical companies that operate in many areas of the world. For such transnational corporations, there is an obvious attraction to the use of the same raw materials, equipment, production methods, and quality control tests at all their plants throughout the world. Thus, such companies have an especially strong interest in promoting compatibility in regulatory policies such as those that control stability testing.

STABILITY

Concepts

Stability testing is a routine procedure performed on drug substances and products. It is involved at various stages of a product's development. In early stages, accelerated stability testing (at relatively high temperatures and/or humidities) can be used for some drugs as a ''worst-case'' evaluation to determine what types of degradation products may be found after long-term storage. Testing under less rigorous conditions (those recommended for long-term shelf storage) and slightly elevated temperatures can be used to determine a product's shelf life and expiration dates (2). Stability testing is performed to ensure that drug products retain their fitness for use until the end of their expiration dates (3).

The raison d'être of pharmaceutical testing should be to provide reasonable assurance that the fitness for use of products remains at an acceptable level throughout the period during which they are in the marketplace available for supply to the patient/consumer. It has been suggested by some that the above definition should be extended so that it covers the period until the patient uses the last unit of product. However, since we cannot control how patients store drugs and because we are aware that a significant proportion of patients store pharmaceuticals in a quite inappropriate manner, many pharmaceutical scientists believe this concept to be impracticable. The most likely method of improving storage of drug products by patients may well be in individual counseling by pharmacists.

Stability of a pharmaceutical product may be defined as the capability of a particular formulation in a specific container/closure system to remain within its physical, chemical, microbiological, therapeutic, toxicological, protective, and informational specifications. Although there are exceptions, 90% of labeled potency is generally recognized as the minimum acceptable potency level (4). Stability is also defined as the extent to which a product retains, within specified limits and throughout its period of storage and use (i.e., its shelf life), the same properties and characteristics that it possessed at the time of its man-

ufacture. The criteria for acceptable levels of stability have been reviewed in the form of a table (5,6).

Factors Affecting Product Stability

Many factors affect the stability of a pharmaceutical product, including the stability of the active ingredient(s); the potential interaction between active and so-called inactive ingredients; the manufacturing process; the dosage form; the container/closure system; the environmental conditions encountered during shipment, storage, and handling; and the length of time between manufacture and usage. Environmental properties such as heat, light, and moisture, as well as chemical factors like oxidation, reduction, hydrolysis, or racemization, can all play vital roles in pharmaceutical stability. Degradation reactions in pharmaceutical formulations may depend on such conditions as concentration of reactants, pH, radiation, temperature, catalysts, and so on (7). A number of other factors are listed in the literature. Of all the many environmental factors that can be involved in drug degradation, temperature is the most important one that cannot be controlled by package selection (4).

The stability of a drug product depends on the raw materials used, warehouse and transport facilities, patient/consumer storage, and in vivo stability. The effects of drug product instability include loss of active drug (e.g., nitroglycerin tablets), increase in concentration of active ingredient (e.g., lidocaine gel), change in biological activity (e.g., tablet aging), loss of content uniformity (e.g., flocculation and impaction in suspensions), presence of pathological microorganisms (e.g., contamination of a multiuse cream), loss of pharmaceutical elegance (e.g., yellowing of direct-compression lactose tablets containing an amine drug), production of toxic decomposition products (e.g., conversion of tetracycline to epianhydrotetracycline), and other factors that change fitness for use (e.g., adhesion aging of transdermals) (8).

Expiration Date/Shelf Life

An **expiration date** is defined as the time up to which the preparation will remain stable when stored under recommended conditions. Thus, an expiration date is the date beyond which it is predicted that the product may no longer retain fitness for use. If the product is not stored in accordance with the manufacturer's instructions, then the product may be expected to degrade more rapidly. Strict adherence to the storage requirements specified in the product labeling will help ensure product stability to the manufacturer's labeled expiration date. The manufacturer's expiration date only applies if these storage requirements are met from the time the product leaves the manufacturer until it is supplied to the user (9).

Shelf life is the time during which we have reason to believe that the product, if stored appropriately, will retain fitness for use (>90% of label claim of potency) (10). The expiration date is also defined as the date placed on the container/labels of a drug product designating the time during which a batch of the product is expected to remain within the approved shelf life specification if stored under defined conditions and after which it may not be used (11). The use of kinetic and predictive studies for establishing credible expiration dates for pharmaceutical products is now accepted worldwide. However, prior to about 1950, only qualitative or semiquantitative methods and procedures were commonly used in pharmaceutical studies. Stability study requirements and protocol designs were covered in detail in the standard professional literature (10–13).

Although shelf life in some instances may be estimated by accelerated stability testing protocols, real-time product stability testing is necessary to validate stability claims (14). Additional data pertinent to shelf life may be obtained using the retained samples, from market challenge tests and test distributed samples, and from returned samples (8).

STABILITY TESTING METHODS

Real-Time Stability Testing

In real-time stability testing, the duration of the test period should normally be long enough to allow significant product degradation under recommended storage conditions. Alternatively, if a product is essentially stable, the test should be conducted for a long enough period to indicate clearly that no measurable degradation occurs. At the least, the testing protocol must permit one to distinguish degradation from interassay variation. For example, data may be collected at an appropriate frequency such that a trend analysis may discern instability from day-to-day imprecision. The reliability of data interpretation can be increased by including in each assay a single lot of reference material with established stability characteristics. Sample recovery between assays can be normalized to this reference, minimizing the impact of systematic drift and interassay imprecision. Frequently, however, an appropriate reference material is not available for use as a control. When one measures the stability of a reference material, imprecision may be introduced by changes in both reagents and instrumentation. Ideally,

reagents should be sufficiently stable that a single lot provides unchanging performance throughout the stability study, and instrument performance should remain constant. However, one must monitor system performance and control for drift and discontinuity resulting from changes in both reagents and instrumentation (14).

The time at which the 90% two-sided lower confidence bound intersects at the 90% potency level on the stability plot (percentage of label claim against time) is best termed the conformance period. This length of time must always be greater than the actual shelf life that is assigned to the product. The conformance period may, of course, be any time interval (e.g., 21.3 months, 38.7 months, or 69.5 months). The shelf life is rounded down from the conformance period to give a convenient value (e.g., 18 months, 3 years, or 5 years). Full details of the method of calculation are given in the FDA guidelines (12).

Accelerated Stability Testing

Accelerated stability testing refers to methods by which product stability may be estimated by storage of the product under conditions that accelerate degradation, commonly by an increase in temperature. Stress conditions that accelerate change fall under the general headings of temperature, light, moisture, agitation, gravity, pH, packaging, and method of manufacture. The accelerated method is often used to provide an early indication of product shelf life and thereby shorten the development schedule. This may permit, in some circumstances, the prediction of the stability of the product at ordinary shelf temperature from data obtained by stress testing. A reasonable statistical treatment in accelerated stability projections based on the Arrhenius equation normally requires that at least four stress temperatures be used. Many accelerated stability testing models are based on the Arrhenius equation (15–18):

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

where k is a rate constant at temperature T (in degrees Kelvin), Ea is the activation energy, and R is the gas constant. This equation describes the relationship between storage temperature and degradation rate. Use of the Arrhenius equation permits a projection of stability from the degradation rates observed at high temperatures for some degradation processes (19). When the activation energy is known, the degradation rate at low temperatures may be projected from those observed at "stress" temperatures.

The classical approach in Arrhenius prediction of drug stability uses two sequential steps of linear regression involving (a) a function of drug content versus time to obtain the rate constants k at several elevated temperatures and (b) the relationship of logarithm of mean k versus reciprocal temperature to predict the room temperature rate constant and hence the shelf life of the drug. The classical approach also provides a wide and unsymmetrical 95% confidence interval for the predicted shelf life (20). The time for the lower 95% confidence limit curve about the fitted straight line to reach 90% of the labeled drug content is assigned as the shelf life of the pharmaceutical product (21,22).

The stress tests used in the current International Conference on Harmonization (ICH) guideline (e.g., 40% for products to be stored at controlled room temperature [CRT]) were developed from a model that assumes an energy of activation of about 83 kJ per mole.

A common practice of manufacturers in pharmaceutical industries is to utilize various shortcuts such as bracket tables (23) and, in the past, the Q rule (16).

Q Rule

The Q rule states that a product degradation rate decreases by a constant factor Q_{10} when the storage temperature is decreased by 10°C. The value of Q_{10} is typically set at 2, 3, or 4 because these correspond to reasonable activation energies. For larger shifts in temperature, the rate constant changes exponentially with temperature, and is proportional to $(Q_{10})^n$, where n equals the temperature change (°C) divided by 10. This model falsely assumes that the value of Q does not vary with temperature. More detailed treatments are given by Anderson and Scott (14) and Connors, Amidon, and Kennon (16). This technique is not recommended.

Bracket Tables

The bracket table technique assumes that, for a given analyte, the activation energy is between two limits (e.g., between 10 and 20 kcal). As a result, a table may be constructed showing "days of stress" at various stress temperatures. Readers are requested to view the table in Ref. 14. The use of a 10 to 20 kcal bracket table is reasonable because broad experience indicates that most analytes and reagents of interest in pharmaceutical and clinical laboratories have activation energies in this range (23,24).

For analytes with high activation energies, both bracket tables and the Q rule provide useful information when they are applied conservatively. Use of published

or experimentally derived activation energy values can significantly lower the risks inherent in projecting product shelf life.

The Q rule and the bracket tables were used in the past by some in the pharmaceutical industry for the prediction of shelf life of the product. These methods are not official in either the ICH or FDA stability guidelines.

Retained Sample Stability Testing

One of the most important elements in most stability testing of marketed pharmaceutical products is evaluation of retained stability samples. The usual practice for such studies is that, for every marketed product for which stability data are required, the manufacturer selects stability samples for retained storage for at least one batch a year. If the number of batches marketed exceeds 50, it is probably desirable to take stability samples from two batches. Often, when a new product is first introduced in the market, the manufacturer may decide to take stability samples of every batch. Later, as increased confidence is gained in the stability of the product, the number of batches kept for stability testing is likely to be progressively reduced so that only 2% to 5% of marketed batches are designated as stability sample batches (8).

Stability samples are tested at predetermined intervals. Thus, if a product has a 5-year shelf life, it is conventional to test at 3, 6, 9, 12, 18, 24, 36, 48, and 60 months. This conventional method of obtaining stability data on retained storage samples was termed the **constant interval method** by Carstensen and Rhodes (8), who pointed out some disadvantages of this method earlier (25,26). These authors have proposed use of the fixed date method of stability sample testing, which uses a modified form of the conventional retained sample testing. They also proposed a much more radical change and termed this method **stability testing by evaluation of market samples**. This method involves taking samples already in the marketplace and evaluating stability attributes (27–29). This type of testing is inherently more realistic since it challenges the product not just in the idealized retained sample storage conditions, but also in the actual marketplace.

Cyclic Temperature Stress Testing

The cyclic temperature stress testing method, as explained by Carstensen and Rhodes (30), may provide evidence about the instability not available from isothermal tests. This type of testing is a very useful component in the gamut of tests available to the pharmaceutical scientist for stability testing (1,29) used in development or troubleshooting, but not for routine testing of marketed product. The cyclic temperature stress tests should be designed based on knowledge of the product so as to mimic likely conditions in marketplace storage. The period of the cycle most favored is 24 h since the diurnal rhythm on earth is 24 h, thus marketed pharmaceuticals are most likely to experience such a cycle during storage (31,32).

Carstensen and Rhodes (32) derived an equation relating temperature change to time based on a sine wave function. It was proposed that the maximum and minimum temperatures for the cyclic stress testing should be selected on a product-by-product basis and taking into account such factors as recommended storage temperatures for the product and specific chemical and physical degradation properties. It was also recommended that the test should normally have about 20 cycles.

MEAN KINETIC TEMPERATURE

Concepts

For a USP/NF product, it is expected that, when properly stored, the product can meet monograph specifications at any time during its shelf life. From time to time, health care practitioners have expressed concerns about the environmental stresses to which drug products are exposed throughout the product's lifetime and about whether the exposure will affect the integrity of the product. The concerns include transportation and storage of drug products by manufacturers, wholesalers, and pharmacies. Thus, the stability of the pharmaceutical article is an attribute that must be known. The USP/NF recognized that storage temperature affects stability and thus defined the storage conditions.

The amendment of the USP definition of Controlled Room Temperature in November 1993 includes a requirement for "a mean kinetic temperature calculated at not more than 25°C." The definition of Controlled Room Temperature is as follows (33,34):

> A temperature maintained thermostatically that encompasses the usual and customary working environment of 20°C to 25°C that results in a mean kinetic temperature calculated to be not more than 25°C; and that allows for excursions between 15°C and 30°C that are experienced in pharmacies, hospitals, and warehouses. Articles may be labeled for storage at "controlled room temperature" or at "up to 25°C," or other wording based on the same mean kinetic temperature.

The relationship between CRT and mean kinetic temperature (MKT) for storage and distribution of pharmaceutical articles is given special attention in official publications (11,35). Since degradation rate constants are temperature dependent, the amount of degradation varies with the temperature during a storage period. The use of MKT originally proposed by Grimm and Shepky (36) has become generally accepted as a convenient method of quantifying storage temperatures as they relate to degradation.

The equation for the determination of MKT, known as the Haynes formula, is derived from the Arrhenius equation, relating the degradation rate constants at different temperatures to the activation energy (37). The MKT concept can be applied to many areas of pharmaceutical distribution: manufacturers, warehouses, shippers, hospital and community pharmacies, emergency vehicles, sales representatives' vehicles, and so on. The **mean kinetic temperature** is the single calculated temperature at which the total amount of degradation over a particular period is equal to the sum of the individual degradations that would occur at various temperatures. Thus, the MKT may be considered an isothermal storage temperature that simulates the nonisothermal effects of storage temperature variation (38,39). It is not a simple arithmetic mean. It is always higher than the arithmetic mean temperature (39).

Calculation of Mean Kinetic Temperature

Although there is general recognition in North America, the European Union, and Japan of the utility of the MKT concept, there is still some debate about the exact method by which this value should be calculated, although in many instances the differences in mode of calculation will have little significant effect on the numerical value obtained.

USP Method

The USP method of calculation (40) is shown below. The mean kinetic temperature is calculated from the average storage temperatures recorded over a 1-year period and the running average calculated from the average of weekly high and low temperatures recorded over the preceding 52 weeks. If the exposure of the pharmaceuticals is for a shorter period (as in doctors' cars, patients' cars, sales representatives' cars, etc.), then it is advised to calculate the MKT with frequent recording of the temperature profile.

The mean kinetic temperature is calculated by Haynes' equation:

$$MKT = \frac{\Delta H/R}{-\ln((e^{-\Delta H/RT_1} + e^{-\Delta H/RT_2} + \ldots + e^{-\Delta H/RT_n})/n)}$$

where MKT is the mean kinetic temperature; ΔH is the energy of activation, 83.144 kJ/mol; R is the universal gas constant, 0.0083144 kJ/mol/degree; T_1 is the arithmetic mean of the highest and lowest temperatures recorded during the first time period (e.g., the first week); T_2 is the arithmetic mean of the highest and lowest temperatures recorded during the second time period (e.g., second week); T_n is the arithmetic mean of the highest and lowest temperatures recorded during the nth time period (e.g., nth week), n being the total number of average storage temperatures recorded (52) during the annual observation period; and all temperatures T being absolute temperatures in degrees Kelvin (K).

In reality, of course, not all pharmaceutical products are characterized by degradation energy of activation of 83 kJ/mol. This is the average value based on work by Grimm and Shepky (36) and Kennon (24). Ideally, the value of activation energy ΔH to be used in the calculation should be determined experimentally for any given product. Among various pharmaceutical dosage forms, the activation energy may vary from 5 to 240 kJ/mol. The change in MKT that results from this variation of activation energies is probably relatively small in many instances (39).

FDA Method

The FDA recommends the method of entering both the individual highest and the lowest temperatures (rather than averages) in the equation for the calculation of MKT. This results in entering 104 data points, in contrast to USP's 52 points (13). Bailey and Medwick (40) discussed the characteristics of methods used to calculate MKT. The USP and the FDA methods of calculation of MKT were compared by the authors, taking into consideration the different values for the activation energy (41).

If temperatures are electronically recorded at many times during a day and all the values are used in the calculation of MKT, then there is no difference between the USP and FDA methods.

Mail-Order Temperature Excursions

Factors that may affect the stability of a drug product during shipment include the specific nature of the product, the types of packaging, and variations in environ-

mental conditions during transport. Since many pharmaceutical products are distributed through the U.S. Postal Service (USPS), a study was performed by Black and Layloff (42) that revealed the interior temperature of a black mailbox was 58°C in an ambient temperature of 38°C in St. Louis, Missouri. This result indicates that pharmaceutical products distributed through the postal service may be exposed to temperatures that significantly exceed those normally specified in stability standards. This is especially likely to be a problem for temperature-sensitive (labile) products.

To observe the effects experienced by the packaged pharmaceuticals during the shipment and distribution, the USP recorded the temperatures and humidities experienced by packages during mail-order distribution using packaging temperature and humidity monitoring devices and shipping packages to different parts of the country. On return of the packages, the MKT was calculated. Results of the study showed that only 8.4% of the packages experienced temperature variations within the excursions allowable under the CRT. The remaining packages were exposed to temperatures significantly above the accepted excursion range. While 65.5% of the packages experienced warm conditions (30°C–40°C) during the shipment, the remaining 26.1% experienced excessive heat (>40°C) conditions. In addition, MKT calculations showed that 31.1% of the packages had MKT values above 25°C for periods of 19 to 21 days. Significant spikes in relative humidity (RH) experienced were also reported (43).

The USP team of scientists also tried to determine the extent of physical and chemical changes experienced by the pharmaceutical preparations exposed to typical shipping conditions. Monitoring devices were used for the study. Results of temperature and humidity variations during shipment indicated that about 40% of the articles experienced an MKT greater than 25°C (44). The data presented agreed with previous findings, demonstrating that the pharmaceuticals experienced significant fluctuations in temperature and humidity during shipment.

Recognizing that some products will be especially sensitive to temperature change, the USP proposed a definition for ''labile'' preparations and the shipping and the labeling requirements for such preparations (45).

The data profile of the temperatures experienced during the shipment and distribution can be obtained using such electronic indicators as TempTale 3 (Sensitech, Inc., Beverly, MA), TempTale H (Sensitech), and Cox Lynx (Cox Recorder, Belmont, NC) and chemical indicators such as time temperature indicator (TTI) (Lifeline Technology, Inc., Morris Plains, NJ) and Monitor Mark (3M, St. Paul, MN). The functioning of the indicators was studied by C. C. Okeke et al. (43). It has also been reported by Carstensen et al. that the MKT in Sudan is in excess of that stipulated for the ''dry, hot'' climate zone (46).

STORAGE CONDITIONS

Concepts

The USP compendial monographs specify storage requirements that are to be maintained throughout the shelf life, shipment, distribution, and storage of the article. The USP storage requirements fall into two major categories, specific and nonspecific (33,47). Many monographs include specific storage conditions, such as ''Store in a cool place.'' A survey conducted by the USP revealed that there exist products that do not have any specific storage conditions (48). The USP General Notices section addresses these types of compendial monographs in the discussion of storage under nonspecific conditions.

The storage conditions under the specific requirements are defined using the following terms: freezer, cold, cool, room temperature, controlled room temperature, warm, excessive heat, and protection from freezing. The storage under nonspecific conditions section states that for articles, regardless of quantity, for which no specific storage directions or limitations are provided in the individual monograph, it is to be understood that conditions of storage and distribution (including the shipment of articles to the consumer) include protection from moisture, storage at controlled room temperature, and, when necessary, protection from light (33).

The length of the stability studies and the storage conditions should be sufficient to cover storage, shipment, and subsequent use (e.g., reconstitution or dilution as recommended in the labeling). The accelerated and long-term storage conditions and the minimum time period at submission are listed below.

Conditions	Minimum Time Period at Submission
Long-term testing, 25°C ± 2°C/ 60 ± 5% RH	12 months
Accelerated testing, 40°C ± 2°C/ 75 ± 5% RH	6 months

When significant change occurs due to accelerated testing, additional testing at an intermediate condition

(e.g., 30°C ± 2°C/60% ± 5% RH) may be used (49). The data (from accelerated testing or from testing at an intermediate condition) may be used to evaluate the impact of short-term excursions outside the label storage conditions such as might occur during shipping.

Testing under the defined long-term conditions will normally be every 3 months during the first year, every 6 months during the second year, and then annually. The long-term testing should be continued for a sufficient period beyond 12 months to cover shelf life at appropriate test periods. The additional accumulated data should then be submitted to the authorities during the assessment period of the registration application. The containers to be used in the long-term, real-time stability evaluation should be the same as or simulate the actual packaging used for storage and distribution.

Heat-sensitive products should be stored under an alternative lower temperature condition, which will eventually become the designated long-term storage temperature. When a lower temperature storage condition is used, the 6 months of accelerated testing should be carried out at 15°C above its designated long-term storage temperature. For example, if a product is to be stored long term under refrigerated conditions, accelerated testing should be conducted at 25°C ± 2°C/60% ± 5% RH. The designated long-term testing conditions will be reflected in the labeling and expiration date. A storage temperature range indicated on the label may be used in accordance with relevant national/regional requirements.

For products for which water loss may be important, such as liquids or semisolids in plastic containers, it may be more appropriate to replace the high relative humidity conditions with lower relative humidity, such as 10–20% (11).

Temperature and humidity determines the climatic and storage conditions. Both factors greatly affect the stability of a drug product. However, since the temperature and humidity constantly change—day and night alteration, seasonal variations—considerations regarding the sorption behavior of the drug and the permeability of packaging materials must also be included (50). There are several studies that report the changes in characteristics of tablets (51–57) and other dosage forms on storage.

Climatic Zones

For convenience in assigning shelf life stability, experts have divided the world into four climatic zones (Table 1) (58) based on their MKTs and relative humidities. The zones are characterized with the corresponding storage conditions (59). The criteria and guide values for assignment of a city to the correct climatic zones are listed in Table 2 (60,61).

The basis of the derived storage conditions were climatic values measured in the open. They covered an average time span of 20 years and are therefore taken as representative for each place. These climatic values were then corrected because drugs are not stored in the open. The average values for temperature and partial pressure of water vapor so obtained were provided with a safety factor (61).

Storage Conditions for Zones I and II

About 85% of the trade in pharmaceutical products in the world is undertaken within the areas of the EU, Japan, and the United States. Therefore, it was obviously useful to have one storage condition that could cover all these territories.

Uniform storage conditions are a basic requirement. In the EU, most of the population live in climatic zone I or II; this figure is 99% in Japan and 94% in the United States. Since climatic zone II is a worst-case situation for the EU, most of Japan, and the United States, an MKT of 25°C covers all those areas. The measured conditions in many warehouses are well below the storage conditions for climatic zone II, giving an indication of the safety margin. All areas in climatic zones I and II in the three areas can be covered by one storage condition (thereby naturally including zone I as well), 25°C/60% RH.

Thus, it can be concluded that stability testing in the EU, Japan, and the United States (zones I and II) can normally be performed by applying the same storage conditions (25°C/60% RH for long-term testing and 40°C/75% RH for high temperatures) to contain a safety margin, meaning that the derived shelf lives also have a built-in safety margin (3).

Storage Conditions for Zones III and IV

If a drug substance is to be marketed in climatic zone III, then samples are stored at 30°C/35% RH. If the product is used in climatic zone IV, samples are stored at 30°C/70% RH (62).

COMPOUNDING

Definition

Compounding is the process by which a pharmacist combines, mixes, or alters ingredients to produce a medi-

Table 1

World Climatic Zones Based on Their MKTs and Relative Humidities

Climatic Zone		Definition	Storage Condition
Zone I	N. Europe	Temperate	21°C/45% RH
Zone II	S. Europe, Japan, United States	Mediterranean	25°C/60% RH
Zone III	Sahara	Hot and dry	30°C/35% RH
Zone IV	Central Africa, Indonesia, etc.	Hot and wet	30°C/70% RH

cation for a patient, acting in accordance, or in reasonable anticipation of, a prescription issued by a physician, nurse practitioner, dentist, or some other duly authorized person. Compounding can be as simple as adding a liquid to a manufactured drug powder that has been formulated to produce a solution or a suspension and as complex as the extemporaneous creation of a novel preparation.

During the past decade, there has been a significant increase in the number of pharmacists in the United States who devote a substantial part of their activities to compounding prescriptions, in some instances for a wide variety of drugs and drug delivery systems (63).

FDA Modernization Act of 1997

The FDA Modernization Act of 1997 (64) added a new section (503A) on Pharmacy Compounding to the Federal Food, Drug, and Cosmetic Act (FDC Act). This act also requires the FDA to establish an expert advisory committee on compounding that will assist the FDA in preparing a list of non-USP drugs that may be used in compounding.

The legislation helps to delineate legal aspects of compounding. Specifically, the new section 503A (a) recognizes the triad relationship (patient, physician, pharmacist) as the basis for the practice of compounding, (b) allows for anticipatory compounding, (c) sets criteria for the drug substances to be used in compounding, (d) describes the development of a memorandum of understanding between states and the FDA to address interstate distribution of compounded drugs, and (e) limits advertising and promotion of compounding services. Section 503A, subsection (b) of the FDA Modernization Act of 1997 specifies the compounding of drugs by the licensed pharmacist and licensed physicians.

The FDA has limited authority to regulate pharmacists legitimately engaged in compounding (65).

Stability of Compounded Products

With the increase in recent years in compounded prescriptions, the question most frequently asked is: ''What is the stability of this product after it is prepared?'' In repackaging, diluting, or mixing a product, the pharmacist should have concern about stability. Assurance of sterility of compounded injections or opthalmics is obviously of great importance. The pharmacist is responsible for the HSDs (Sterile Drug Products for Home Use) dispensed that are a commercially available type or a compounded product from dispensing to the patient until the consumer uses it, passing through the phases of distribution and storage (66).

As a final step in meeting responsibility for the stability of drugs compounded or dispensed, the pharmacist is

Table 2

Criteria and Guide Values for Assignment of a City to the Correct Climatic Zones

	Guide Values for Individual Climatic Zone			
Criteria	I	II	III	IV
Mean annual temperature measured in the open air	Up to 15°C	>15–22°C	>22°C	>22°C
Calculated mean annual temperature (<19°C)	Up to 20.5°C	>20.5–24°C	>24°C	>24°C
Mean annual water vapor partial pressure	Up to 11 mbar	>11–18 mbar	Up to 15 mbar	>15 mbar

obligated to inform the patient regarding the proper storage conditions (for example, keeping the drug in a cool dry place—not in the bathroom), for both prescription and nonprescription products, and for providing a reasonable estimate of the time after which the medication should be discarded. When expiration dates are applied, the pharmacist should emphasize to the patient that the dates are applicable only when proper storage conditions are used. Patients should be encouraged to clean out their drug storage cabinets periodically (5).

Compounded products pose a new set of concerns because the pharmacist does not always have extensive stability data. Trissel has proposed some stability monographs for a number of compounded drug products (67). The stability of compounded products is defined to be the same as that of manufactured products listed officially in the USP (35). Compounded preparations should be packaged in containers that meet USP standards. The information regarding the containers for packaging is dealt in detail in Sections <661> and <671> of USP 23.

The safety, efficacy, and other quality attributes of compounded preparations depend on correct ingredients and calculations, accurate and precise measurements, appropriate formulation conditions and procedures, and prudent pharmaceutical judgment. The pharmacist should review each procedure in the compounding process to ensure accuracy and completeness; the pharmacist should be prepared to conduct such tests as may be necessary for any given product (68).

Beyond-Use Date

The ICH Stability Guidelines (1993) provide uniform test conditions of temperature and humidity for stability testing of drug substances and products (69,70). With the establishment of these uniform test conditions of temperature and humidity for stability testing, a reexamination of the 1991 beyond-use dating proposals took place, and the revised form was published in 1996 (71).

The beyond-use date is a means of making available to pharmacists some reliable information for indicating to patients the date after which a prescribed medication should not be used. The beyond-use date applies to all the medications that are not dispensed directly from manufacturers, such as medications that are repackaged and/or compounded and dispensed by the pharmacist. Because compounded preparations are intended for administration immediately or following short-term storage, their beyond-use dates may be assigned based on criteria that are not always identical to those used in assigning expiration dates for manufactured drug products. Beyond-use dates should be assigned conservatively.

The pharmacist is responsible to allot a justifiable beyond-use date for the compounded/dispensed product based on reliable information such as that available from pharmaceutical manufacturers, literature on the compounded product's stability, or the USP. All stability data must be carefully interpreted in relation to the actual compounded formulation. In addition to using all available stability information, the pharmacist will also use his or her pharmaceutical education and experience in allotting the beyond-use date for the compounded formulations.

Bailey and Medwick reported the available methods of securing data on which to base a beyond-use date (72,73). The manufacturers may conduct the ''open dish'' studies (apart from other stability studies) to obtain the data needed to provide the pharmacist with the information on dispensing container selection and beyond-use date recommendations for solid dosage forms. The open dish study is a study in which the dosage forms are exposed to 60% RH at 25°C for 30 days without any container protection; three samples of 30 unit doses from one lot are analyzed at 0 and 30 days. A detailed procedure for conducting the open-dish studies was published in the Pharmacopeial Forum (74).

In the absence of stability information that is applicable to a specific drug preparation, it is recommended that, for nonsterile nonaqueous liquids and solid formulations, the maximum beyond-use date should not be later than 25% of the time remaining until the product's expiration date or 6 months, whichever is earlier (when packed in tight, light-resistant containers and stored at CRT unless otherwise indicated). For nonaqueous formulations, a maximum period of 14 days is recommended for determining the beyond-use date when stored at cold temperatures.

Federal law requires that the label on the container or package of an officially compounded preparation must bear a beyond-use date. Good pharmacy practice dictates beyond-use labeling for all compounded preparations.

CONCLUSION

Pharmaceutical scientists and regulators may justifiably feel a sense of achievement when they review the progress that has been made in stability testing in recent decades. The increasing attention now being given to the possible effects of storage and transport on the stability of pharmaceutical products (manufactured or compounded) is well deserved and, it is hoped, will lead to an improved level of confidence about the quality of drug products that are supplied to patients.

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