Drug Development and Industrial Pharmacy, 25(7), 831–856 (1999)

Regulatory Aspects of Stability Testing in Europe

Brian R. Matthews

Director, EC Registration, Alcon Laboratories (UK) Limited, Pentagon Park, Boundary Way, Hemel Hempstead HP2 7UD, England

ABSTRACT

The stability data requirements for human pharmaceuticals in the European Community (EC) are based on a series of Directive and Regulation requirements and on a series of advisory guidelines that have been developed and adopted through the International Conference on Harmonization (ICH) procedures or, where there is no relevant ICH project, through the Committee for Proprietary Medicinal Products (CPMP). There are relevant requirements that cover new drugs and finished products containing them and also for existing active ingredients and products containing them. The sources of the relevant information and the data requirements are discussed and summarized.

INTRODUCTION

The stability of pharmaceutical ingredients and the products containing them depends on (*a*) the chemical and physical properties of the materials concerned (including the excipients and container systems used for formulated products) and (*b*) environmental factors such as temperature, humidity, and light and their effect on the substances in the product. Stability data on the drug substance and the formulated product are required in connection with applications for marketing authorizations for pharmaceutical products containing new active substances, for products containing known active substances (including reformulations), for additional strengths or dosage forms, for new containers, and for amendments or variations to existing marketing authorizations, including new sources for active ingredients, extensions to the shelf life, and so on. In this paper, the general regulatory requirements for stability testing of pharmaceuticals for registration in the European Community (European Union) are discussed with respect to the sources of information on stability requirements, the design of stability studies for new drug substances and finished products (drug products) containing new and known (pharmacopoeial or other) active ingredients, the presentation of stability data, and conclusions.

In the context of pharmaceutical products, *stability* should be considered not in the dictionary definition sense of ''fixed'' or ''not likely to change,'' but in the sense of ''controlled, documented and acceptable change.'' The types of change that have to be taken into account include chemical, physical, pharmacotechnical, microbiological, toxicological, as well as changes to bioavailability and other clinically significant changes. An

important question then becomes: What degree of change is acceptable?

This question needs to be addressed in the marketing authorization application. In arriving at an answer that is mutually acceptable to the pharmaceutical manufacturer and the regulatory authorities, due account will need to be taken of the body of available evidence and theoretical extrapolations based on known physical and chemical laws and statistical models. However, many of the final proposals are often based on subjective, rather than objective, assessment of data, and the basis for decisions should therefore be discussed in the application.

In addition to the need for these data, at the time of marketing authorization application it should be kept in mind that there are also requirements for stability data generation in connection with other parts of the regulatory process. This includes data generation during the conduct of safety studies under good laboratory practice conditions (e.g., the stability of the drug in the medium being used for administration in animals and the stability of the radiolabel used in tracer studies), for clinical trial approvals in many countries (in which both the investigational product and any active comparator may need to be investigated for stability), as well as for preclinical and clinical studies (for which the stability of the analyte in biological specimens may need to be investigated in addition to the stability of the product under test).

In addition, such studies may be needed to meet good manufacturing practice requirements (including the retention of reference samples and starting materials) after the product has been approved for marketing, to undertake stability studies on manufactured batches, and to meet the requirements of the rapid alert system with respect to products that have stability problems during distribution. Medicine inspectors may also request to see data being generated at the request of assessors, including ongoing stability investigations.

Some of the types of change in pharmaceutical products that may need to be considered (depending on the dosage form concerned) are

- *Physical changes*: appearance, consistency, product uniformity, clarity of solution, absence of particulates, Color, odor or taste, hardness, friability, disintegration, dissolution, sedimentation and resuspendability, weight change, moisture content, particle shape and size, pH, package integrity
- *Chemical changes*: degradation product formation, loss of potency (active ingredient), loss of excipients (antimicrobial preservatives, antioxidants)
- *Microbial changes*: proliferation of microorganisms in nonsterile products, maintenance of sterility, preservative efficacy changes

In designing a stability program, due account should be taken of the nature of the ingredients and the finished product, the intended clinical uses, and any special factors.

The discussion in this paper centers on consideration of the requirements that apply to pharmaceutical products containing chemical active ingredients intended for use by humans. However, stability data are required for all types of products subjected to a regulatory procedure under the terms of the EC Pharmaceutical Directives, including homoeopathic products, herbal products, immunological products, biological products, products derived from biotechnology, and veterinary medicinal products. There are a number of specific sources of information on the data requirements for these classes of products, but these are not discussed here.

In addition, a summary of World Health Organization (WHO) stability study recommendations is included, as is a glossary of stability-related terms.

REASONS FOR STABILITY STUDIES

Stability data are produced to establish the storage conditions and retest interval of the active ingredient and the storage conditions and shelf life for the manufactured products. Part of the information can also be used to justify overages included in products for stability reasons. When sufficient data are not available to support fully a desired shelf life, it is open to the manufacturer to base an application on the available information, but to offer an ongoing commitment to generate additional data and to advise the regulatory authority should any value then fall outside the agreed specifications.

In its recently adopted stability guidelines, the Committee for Proprietary Medicinal Products (CPMP) indicates that the objective of stability testing is ''to provide evidence on how the quality of an active substance or medicinal product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, and enables recommended storage conditions, re-test periods and shelf-lives to be established'' (1).

PHARMACEUTICAL EXPERT REPORTS: DISCUSSION OF STABILITY DATA

The pharmaceutical Expert Report is an important tool in the regulatory submission in Europe and can be used

to present a rationale and justification for the proposals made in the application, not least concerning any unusual or controversial aspects of stability data or shelf life proposals. In the case of a request for a shelf life based on limited experimental data, the Expert should put forward an opinion on the reasonableness of that request.

In addition, the pharmaceutical Expert Report should provide a critical assessment of all other relevant data, as well as a summary of the data in the main file, and could include a discussion of the points below.

For active ingredients,

- a summary of the results and an analysis of the data;
- the variability of the stability profiles of different batches of drug substance;
- the most appropriate storage conditions for the active ingredient;
- the proposed duration of storage before retesting;
- the significance of the degradation products that can form on storage with cross references to the relevant information in the pharmacotoxicological Expert Report; and
- the reasonableness of the specification proposed for the active ingredient in relation to the available batch analysis, the analytical methods used and their validation, and the available stability data.

For finished products,

- a discussion of the basis for the relevance of the data included in the marketing authorization application other than those relating to the intended marketing formulation and proposed marketing packaging;
- discussion of data relating to the potential effects of manufacturing procedures (such as heating, exposure to ionizing radiation, etc.) on the stability of the active ingredient or the finished product;
- a summary of the results of the stability trials and an analysis of the data, particularly the assay results for the active ingredient and the content of significant degradation products;
- commentary on any inconsistencies in the data;
- a discussion of the variations in stability found between batches of the finished product;
- an explanation of the calculations used to estimate the shelf life from the stability test data;
- a justification for any excesses in the quantities of active ingredients (and excipients if appropriate) in the manufactured products indicating whether they are there because of stability reasons or to cover manufacturing losses;
- discussion of the proposed finished product specification, particularly a justification for the release specification limits (with cross references to appropriate sections of the pharmacotoxicological data or Expert Report); and
- a justification for the proposed finished product storage conditions and shelf life in the light of the supporting data, particularly for the shelf life of a reconstituted or diluted product, and a commentary on the specific instructions for the preparation of the material that will be administered (particularly products administered by infusion).

There should also be an interplay between the stability section and other parts of the marketing authorization application. For example, the pharmaceutical Expert Report may need to discuss a number of items included in the development pharmaceutics section of the application in the context of the stability data, for example:

- compatibility of the active ingredients and the excipients used in the formulated product and compatibility of the excipients with each other;
- physical parameters such as the effect of pH within the specified range (including potential effects on active ingredients, antimicrobial efficacy, etc.) and any long-term effects observed in the stability studies;
- dissolution performance of conventional release products—the data in the development pharmaceutics and stability sections can be discussed by the pharmaceutical Expert when considering whether a dissolution test should form part of the routine finished product test specification;
- a discussion of the potential for interaction, particularly between semiliquid and liquid manufactured products (including aerosols) and their container/closure systems (sorption or leaching) and other products (such as administration sets) with which the products must be used in clinical practice, and proposals for or justification of any proposed statements for inclusion in the summary of product characteristics or patient information leaflet; and
- discussion of the potential impurities that could be present in the active ingredient and the product, including synthetic by-products; impurities from starting materials or isomerization; residual solvents, reagents, or catalysts and degradation prod-

ucts and the adequacy of the analytical methods used in the stability studies with respect to their specificity, and so on. The availability (or otherwise) of synthesized reference materials for potential degradation products and/or other impurities may need to be discussed.

When a product contains a novel pharmaceutical excipient, full data may be required as for a new active ingredient. In such cases, stability data (including tests relevant to the intended performance of the novel material) will also be required for the excipient, as well as for the product containing it. The pharmaceutical Expert should discuss the data and their adequacy.

POSTMARKETING CHANGES

Even after an application has been approved and the product has been placed on the market, consideration has to be given to the effects of changes to the manufacturing formula or manufacturing processes in the light of production experience. Bioequivalence of the product and stability changes may be affected. Appropriate studies will therefore need to be undertaken, and applications for variations will need to be submitted as necessary. The current data requirements for such applications are discussed below.

DRUG-DEVICE COMBINATIONS

For Europe, in the case of medical devices containing an integral substance that in other circumstances would be a medicinal product, stability data will be required as part of a file that will have to be submitted to a ''notified body'' and that will be referred in part to a pharmaceutical competent authority for consideration of matters relating to the ''pharmaceutical'' material. In the case of medical devices supplied with a pharmaceutical as a single nonreusable unit, the pharmaceutical regulatory regime will apply.

In both cases, the type and extent of data that the regulatory agency examining the dossier will expect are likely to be similar. However, for some types of medical device, specific advice on stability studies may be available in the form of European Committee for Standardization (CEN) or International Organization for Standardization (ISO) standards (for example, for contact lens care products).

SOURCES OF INFORMATION

The primary sources of regulatory requirements in the European Community are the pharmaceutical Regulations and Directives. In addition, there is guidance on how to meet those requirements in a series of advisory guidelines. The relevant documents can now be accessed through the Internet.

There are two primary sites of relevance. The first is EudraLex at http://dg3.eudra.org/eudralex, which has all of the relevant documents for human medicines that form the *Rules Governing Medicinal Products in the European Union* in portable document format (PDF), but some only in read-only format. Second, the CPMP and International Conference on Harmonization (ICH) draft and adopted guidelines on the European Agency for the Evaluation of Medicinal Products (EMEA)/CPMP home page at www.eudra.org, which has PDF copies of the documents (which are printable). Hard copies of the EudraLex documents can be purchased from agents of the EU's Office for Official Publications. The CPMP adopted and draft guidelines may be purchased from a number of commercial sources, including the Medicines Control Agency (MCA) EuroDirect service and professional associations such as the Regulatory Affairs Professionals Society (RAPS) and Drug Information Association (DIA), as well as obtained from trade associations.

As indicated above, in the case of data requirements in the stability area, there are a number of documents that need to be studied, with specific information in the annex to Directive 91/507/EEC (which is actually a replacement for the annex of Directive 75/318/EEC), as well as various guidelines on stability testing, including the primary guideline for requirements applying to new drug substances and products containing them that was adopted through the ICH process, several secondary ICH guidelines, CPMP guidance on stability issues, some relevant references included in the body of other guidelines (CPMP or ICH), the requirements built into the Variations Regulation, and so on. A list of relevant documents is included at the end of this paper. Each of the main sources of information is discussed below.

Directives

Articles 4 and 4a of Directive 65/65/EEC require the submission of results of physicochemical, biological, or microbiological tests, pharmacological and toxicological tests, and clinical trials. Data on stability and storage need to be included in the application for a marketing authorization to support the information included in the section

of the Summary of Product Characteristics on shelf life and precautions for storage (Article 4a of Directive 65/65/EEC). When reliance is placed on a European Drug Master File (DMF) rather than inclusion of data in the application itself, it should be borne in mind that stability data on the active ingredient will need to be included in the DMF.

Directive 91/507/EEC introduced a formal requirement for *all* analytical methods used in connection with a marketing authorization application to have been validated and for the validation data to be included with the dossier. This includes the analytical methods used in the development pharmaceutics and stability sections of the file. The number of replicates of individual determinations undertaken for validated methods should be related to the results of the validation studies. Revalidation of methods may be required when, for example, significant changes to the method of manufacture of the active ingredient or changes to the composition of the finished product have occurred.

Guidelines

Several guidelines should be taken into account by those undertaking stability tests for submission in a European marketing authorization application. The European Community's CPMP adopted a guideline on stability testing in July 1988, and this came into effect in 1989. For new active ingredients and products containing them, this in effect has been replaced by the guideline adopted through the ICH process, and it is expected that all applications submitted since 1998 will include studies that have been conducted according to the ICH-derived guideline. A revision of the old CPMP stability guideline (the new one relating to requirements for stability data required for existing active ingredients and products containing them) was adopted in April 1998, with an operational date of October 1998. At the same time, a guideline was adopted on the data requirements for a type II variation to a marketing authorization.

In addition to the main ICH stability guideline, recent documents include a note for guidance on photostability testing and another for new dosage forms (of new active substances). More details of the guideline content is given below.

DATA REQUIREMENTS

As indicated above, all analytical methods should be adequately validated. For stability studies, it is important that the analytical methods are capable of detecting and quantitating degradation products and interaction products (active ingredient/excipient and/or active ingredient/container components) in the finished product and should also be capable of separating these from substances unique to the active ingredient (e.g., synthetic impurities that are not degradation product). The basic requirements for information to be included in a marketing authorization application on stability of the active ingredients and the manufactured product are summarized below.

For active ingredients,

- information on the batches tested (including date and place of manufacture, batch size, and use of batches);
- details of the test methodology, including normal, stress, and accelerated conditions, as appropriate;
- analytical test procedures and their validation data, with particular reference to the assay and the determination of degradation products;
- analytical results, including initial results;
- conclusions;
- a proposed retest interval and storage conditions for the ingredient.

For dosage forms,

- proposed specification to apply at the end of the shelf life (the release specification being included elsewhere in the dossier), including the acceptable limits for impurity or degradation product content following storage under the recommended conditions;
- batches tested and the packaging used, including details of the composition (if not that of the proposed marketing formula), packaging, batch manufacturing date and site, batch size, and use of batch;
- study design and methods for real-time and accelerated conditions;
- characteristics studied, including physical, microbiological, chemical, chromatographic, and the like characteristics of the product, as well as characteristics of the product such as potency and purity, and including potential interactions between the container and closure system and the product, as well as characteristics such as preservative efficacy and sterility in appropriate cases;
- evaluation of the test procedures, including description and validation, and consideration of potential interference in the test results;

- test results, including initial results, and information on degradation products;
- discussion of the available information regarding compatibility and stability with administration devices such as infusion sets and syringes, for example;
- conclusions;
- proposed shelf life and storage conditions, including the shelf life after reconstitution or after first opening of the product, and simulated in-use stability data.

Information should also be provided in the application regarding any ongoing stability studies.

Physical characteristics such as crystal form, moisture content, and particle size may need to be considered for the formulated product. These may have an effect on bioavailability, content uniformity, suspension properties, and possibly patient comfort (e.g., for ophthalmic products). Critical characteristics may need to be controlled in the finished product specification.

When a chiral substance is used in a pharmaceutical product, both the raw material and the finished product containing it should be investigated for the absence of unacceptable changes in the stereochemical purity or ratio during the proposed retest interval and shelf life.

For some dosage forms, particular aspects of stability testing may need to be given particular attention. Examples include the formation of particulates on storage in products intended for intravenous infusion; the stability of intravenous additives in the diluents proposed for use; the stability characteristics of aerosol inhalation products (especially when these have been reformulated to replace chlorofluorocarbon propellants). Products in plastics containers (especially for semisolid/liquid products, including aerosol inhalation, parenteral, and ophthalmic products) will require special consideration, particularly with respect to protection of the product from external factors, extraction of materials from the polymer, or release of materials from polymers (including antioxidants, mono- and oligomers, plasticizers, catalysts, processing aids, mineral compounds such as calcium, barium, or tin, etc.); and relating to the rate of moisture vapor loss and the tightness of closures, for example.

Impurities in New Active Substances

The ICH guideline on impurities in new active substances requires characterization of recurring impurities and degradation products found at or above an apparent level of 0.1% (e.g., calculated with reference to the response factor of the drug). When it is not possible to identify an impurity, a summary of the studies undertaken to try to make such identification should be included in the dossier. Data may also be reported regarding studies undertaken on impurities present below 0.1%, although this is not normally required unless the potential impurities are expected to be unusually potent or toxic or to have pharmacological activity. However, analytical values between 0.05% and 0.09% should not be rounded up when reporting study results.

Impurities in New Medicinal Products

A second ICH guideline addresses impurities in new medicinal products. The degradation products of the active ingredient or reaction products between the active ingredient and excipients or container components, but not impurities arising from excipients, or extraneous contaminants (which should not be present and which should be the subject of good manufacturing practice controls), observed during stability trials under the recommended storage conditions should be reported, identified, and/or qualified when suggested thresholds are exceeded.

The suggested thresholds are as follows:

Maximum daily dose	Threshold for reporting
$\leq$ 1 g	0.1%
$>$ 1 g	0.05%

Regarding the threshold for reporting, the degradation test procedure can be an important support tool for monitoring the manufacturing quality, as well as for use in setting a shelf life for the product, and the reporting level should be set below the level of the identification threshold.

Maximum daily dose	Threshold for identification
$<$ 1 mg	1.0% or 5 μg total daily intake, whichever is lowest
1–10 mg	0.5% or 20 μg total daily intake, whichever is lowest
$>$ 10 mg–2 g	0.2% or 2 mg total daily intake, whichever is lowest
$>$ 2 g	0.1%

Maximum daily dose	Threshold for qualification
$<$ 10 mg	1.0% or 50 μg total daily intake, whichever is lowest
10–100 mg	0.5% or 200 μg total daily intake, whichever is lowest
$>$ 100 mg–2 g	0.2% or 2 mg total daily intake, whichever is lowest
$>$ 2 g	0.1%

Higher thresholds may be proposed (with justification) if the target reporting threshold cannot be achieved. When it is not possible to identify particular degradation products, a summary of the studies undertaken should be included in the application. However, these requirements will affect the design of stability studies, particularly the choice of analytical method.

Identification should also be considered for particularly potent, toxic, or pharmacologically significant degradation products below the stated levels. The specification for the finished product should include limits for degradation products known to occur under the stated storage conditions and should take into account the qualification of those substances. The basis for the proposals should be data on the product intended to be marketed. A rationale should be given for the inclusion and exclusion of impurities from such specifications.

Stability Testing of New Drug Substances and Products

The guideline, Stability Testing of New Active Substances and Medicinal Products, was adopted by the CPMP in December 1993 after the usual ICH development process and may be considered as the ''parent'' ICH guideline. It is expected to be used as the basis for stability trials reported for all applications for new drugs and products containing them from January 1, 1998 (particularly for the provision of data on the required number of batches with the use of long-term testing conditions of 25°C and 60% relative humidity [RH] for 12 months and accelerated testing at 40°C and 75% RH for 6 months with testing under controlled humidity conditions), but also was accepted for earlier submissions. (For abridged applications, the CPMP guideline on stability testing of existing active substances and related finished products was adopted in April 1998 and had an operational date of October 1998. It was based closely on the parent ICH guideline.)

Sampling and specific test requirements for particular dosage forms or packaging etc are not covered by the ICH guidelines.

The ICH guideline was developed taking into account the concept of climatic zone and conditions (Table 1). The ICH regions are encompassed by climatic zones I and II.

General

Stability studies (conditions and duration) should be of sufficient duration to cover storage, shipment, and subsequent use (including reconstitution or dilution of the finished product if appropriate). The use of the same storage conditions for the drug substance and the finished product facilitates comparisons of the data generated, although other justified storage conditions can be included.

The recommended storage conditions are as follows:

Test	Conditions	Minimum period
Long term	25°C ± 2°C 60% ± 5% RH or *t*°C ± 2°C and appropriate RH	12 months; extended to cover retest interval or shelf life
Intermediate (example)	30°C ± 2°C 60% ± 5% RH	6 months of data from 12-month study
Accelerated	40°C ± 2°C 75% ± 5% RH or (*t* + 15)°C ± 2°C and appropriate RH	6 months

It would normally be expected that data would be generated at 25°C and at 40°C, but alternative justified conditions will be accepted, for example, in the case of products with normal storage conditions that would be lower than 25°C (*t*°C), in which case the accelerated condition would be (*t* + 15)°C. The intermediate condition would be used when ''significant change'' (i.e., failure to meet the proposed or agreed specification for an active substance) or (*a*) a 5% loss of potency from the initial batch analysis of the finished product, (*b*) the level of a specified degradation product exceeded its specification limit, (*c*) the product exceeded its pH limits, (*d*) the dissolution performance fell outside the specification, or (*e*) there was a failure to meet specifications for appearance or physical properties (color, phase separation, resuspendability, delivery per actuation, caking, hardness, etc.) occurred during accelerated testing or when a product was not suitable for testing at that temperature (e.g., an eye ointment designed to melt below 40°C). The data at 30°C and/or 40°C can be used to evaluate the effect of short-term excursions outside the labeled storage conditions (e.g., during shipping).

Other storage conditions may be used if justified. Special consideration should be given to products that change physically or chemically at lower storage conditions, such as suspensions and emulsions (which may cream or sediment) or creams, oils, or semisolid preparations that may increase in viscosity. Conditions of high relative humidity are particularly applicable to solid dos-

Table 1

International Climatic Zones and Conditions (CPMP Stability Guideline)

Climatic Condition	Zone I: Temperate (e.g., Northern Europe, United Kingdom, Canada, Russia)	Zone II: Mediterranean (Subtropical) (e.g., United States, Southern Europe, Japan)	Zone III: Hot/Dry or Hot/Moderate RH (e.g., Iran, Iraq, Sudan)	Zone IV: Very Hot/Humid (e.g., Brazil, Ghana, Indonesia, Nicaragua, Philippines)
Mean annual temperature	<20.5°C	20.5°C–24°C	>24°C	>24°C
Kinetic mean temperature	21°C	26°C	31°C	31°C
Mean annual relative humidity (%)	45%	60%	40%	70%

age forms or other products in packs designed to offer a permanent barrier to moisture vapor loss; aqueous solutions, suspensions, and the like packaged in semipermeable containers may be tested under low relative humidity conditions (e.g., 10–20% RH). It is understood that, at least for the United States and Europe, the long-term test conditions for semipermeable containers should be 25°C ± 2°C at 40% RH ± 5% RH, and accelerated conditions should be 40°C ± 2°C at 10–20% RH, although this is due to be reconsidered during the revision of the ICH guideline.

The testing intervals should be sufficient to establish the stability characteristics of the drug substance and the dosage form. The suggested sampling frequency is every 3 months for the first year and then every 6 months for the second year and annually thereafter.

The long-term studies should be undertaken in packaging that is intended for storage and distribution or material that simulates that packaging for drug substances. Containers and closure systems used in primary stability studies of finished products should be those intended for marketing.

Matrixing or bracketing studies may be applied if justified. This is discussed in a separate section.

Stability tests should be designed to cover those features of the active ingredient or finished product that are susceptible to change during storage. The information collected should cover any factor that is likely to affect quality, safety, or efficacy, including chemical, physical, and microbiological characteristics.

The limits of acceptability in the proposed specifications should be derived from the stability profiles obtained. The specification will need to include individual and total upper limits for impurities and degradation products. Justification for the proposed levels will need to include reference to the levels of the impurities and degradation products that were present in the materials used in preclinical and clinical studies (i.e., whether or not they have been ''validated'').

Drug Substance

In addition to the accelerated and long-term studies, stress tests of the drug substance should also be used. These should be designed to determine the intrinsic degradation pathways and to identify likely degradation products and show the suitability of the analytical procedures.

Three batches of drug substance, prepared at not less than pilot manufacturing scale utilizing the intended synthetic route to be used for commercial material, should be used to evaluate stability. The data obtained are used to establish a retest interval. The batches tested should also be representative of the quality of the material used in preclinical and clinical studies, as well as the intended manufacturing-scale material. Laboratory-scale batches can be used for supporting data. The first three production batches should be placed in a long-term study if these data are not included in the submission; the study should use the same stability protocol reported in the dossier.

For quantitative characteristics expected to decrease with time, it is suggested that the time at which the 95% one-sided confidence limit for the mean degradation curve intersects the acceptable lower specification limit be used to establish this interval. Data may be combined if the batch-to-batch variability is small and if satisfactory results are first obtained from statistical tests applied to the regression lines and zero time intercepts for the individual batches (e.g., if the p value for the level of significance of rejection is more than 0.25). Depending on the degradation relationship, the data may be transformed (e.g., using linear, quadratic, or cubic functions) for linear regression analysis using arithmetic or logarithmic scales; statistical tests should be applied for the good-

ness of fit of the data to the assumed degradation plot. When it is not possible to combine data, the retest interval may be established according to the least stable batch.

When there is little degradation or little variability, formal statistical analysis of the data are not usually required if visual examination is sufficient.

Limited extrapolation of real-time data (especially when supported by accelerated data) may be allowed. This should be justified by reference to the mechanism for degradation, the goodness of fit of the statistical model, the batch sizes concerned, and available supporting data. The justification should take into account assay results and levels of degradation products and any other relevant characteristics.

The storage conditions for inclusion in the labeling should be in accordance with local regulatory requirements based on a consideration of the stability data. Specific warnings should be included (e.g., ''Do not freeze''). Terms such as ''ambient conditions'' and ''room temperature'' should be avoided.

Finished Product

The information on the stability of the drug substance and data on the clinical trial formulation should be taken into account in designing stability studies for the dosage form of the finished product. The chosen design should be justified.

The stability studies of the finished product should be conducted on at least three batches of the formulation proposed for marketing; the batches should be made by a process that meaningfully simulates the intended commercial process (and ideally uses separate lots of the active ingredient) in the intended commercial container system. Two of the batches should be at least of pilot-scale manufacture (i.e., representative of and simulating the full-scale production process, such as a minimum of $^1/_{10}$ scale or 100,000 tablets or capsules). A third batch may be smaller (e.g., 25,000–50,000 tablets or capsules). The same quality specification should apply as that proposed for the commercial product. If appropriate data are not submitted with the application, the first three production batches should be placed on accelerated and long-term stability tests using the same protocol as that reported in the application.

Data on laboratory-scale batches are not normally acceptable as primary data. They may be used to support primary data, as may information on products with related, but not identical, formulations and/or different packaging.

The presentation and evaluation of the data should be systematic and should cover necessary physical, pharmacotechnical (e.g., dissolution), chemical, biological, and microbiological attributes. The degree of variability of the data from the tested batches will affect the confidence that future production batches will meet the specification to the end of their shelf life.

For quantitative characteristics expected to decrease with time, it is suggested that the time at which the 95% one-sided confidence limit for the mean degradation curve intersects the acceptable lower specification limit be used to establish this interval. Data may be combined if the batch-to-batch variability is small and if satisfactory results are first obtained from statistical tests applied to the regression lines and zero time intercepts for the individual batches (e.g., if the p value for the level of significance of rejection is more than 0.25). Depending on the degradation relationship, the data may be transformed (e.g., using linear, quadratic, or cubic functions) for linear regression analysis using arithmetic or logarithmic scales; statistical tests should be applied for the goodness of fit of the data to the assumed degradation plot. When it is not possible to combine data, the retest interval may be established according to the least stable batch.

When there is little degradation or little variability, formal statistical analysis of the data are not usually required if visual examination is sufficient.

Limited extrapolation of real-time data (especially when supported by accelerated data) may be allowed. This should be justified by reference to the mechanism for degradation, the goodness of fit of the statistical model, the batch sizes concerned, and available supporting data. The justification should take into account assay results and levels of degradation products and any other relevant characteristics.

The storage conditions for inclusion in the labeling should be in accordance with local regulatory requirements based on a consideration of the stability data. Specific warnings should be included (e.g., ''Do not freeze''). Terms such as ''ambient conditions'' and ''room temperature'' should be avoided. However, see the discussion of specific European requirements for labeling and leaflets, later.

International Conference on Harmonization Guideline: Stability Testing: Requirements for New Dosage Forms

The ICH guideline, Stability Testing: Requirements for New Dosage Forms (an annex to the parent ICH stability guideline), was adopted by the CPMP in December 1996 and came into operation for studies commencing after January 1998. It is addressed to the manufacturer

of the originally approved product and applies to applications for new dosage forms (i.e., a different pharmaceutical product type, including products intended for different routes of administration, e.g., oral to parenteral; and different functional types, e.g., immediate-release tablets to modified-release tablets; and different dosage forms for the same route of administration, e.g., capsules to tablets or solutions to suspensions) containing the same active ingredient as the approved product. Such products should, in principle, follow the main guideline, but it might be possible in justified cases to provide a limited amount of data at the time of submission, such as 6 months of accelerated and 6 months of long-term data from ongoing studies.

International Conference on Harmonization Guideline: Photostability Testing of New Drug Substances and Products

The ICH document, Photostability Testing of New Active Substances and Medicinal Products was adopted by the CPMP in December 1996 and came into effect for studies commencing after January 1998. It is an annex to the parent ICH stability guideline.

The guideline is intended to be taken into account when designing light challenge tests and stress tests for marketing authorization applications for new active substances and products containing them, but may also be used in connection with variation applications for formulation or packaging amendments. However, photostability testing is not required as a part of the stability test program for marketed products. The guideline does not address in-use photostability of products (but see below) or extend to products not covered by the parent stability guideline.

Photostability tests are normally undertaken on a single representative batch of the material under consideration, although this may need to be extended if certain changes are made to the product (e.g., to the formulation or the packaging) or depending on the data initially reported concerning photostability.

The approach to the test should be systematic and involve (*a*) tests on the drug substance; (*b*) tests on the formulated product outside its immediate pack; (*c*) tests on the drug product in the immediate pack if there are signs of photolability in this condition, and (*d*) tests on the finished product in the marketing pack if there are signs of instability in this configuration. The applicant should define and justify the limits of acceptable change, and this will determine the extent of photostability testing required. Any resulting labeling requirements are those required by the relevant regulatory authority.

The light sources to be used for photostability studies and described in the guideline are (*a*) one producing an output similar to the D65 (outdoor daylight, ISO 10977: 1993)/ID65 (indoor indirect daylight) emission standard (such as an artificial daylight fluorescent lamp combining ultraviolet [UV] and visible outputs, xenon, or metal halide lamps) with a window glass filter for a device having a significant output below 320 nm or (*b*) exposure of the same sample to both a cool white fluorescent lamp designed to produce an output similar to that specified in ISO 10977:1993 and a near-UV fluorescent lamp having a spectral distribution from 320 nm to 400 nm with maximum energy emission between 350 nm and 370 nm and a significant proportion of output in bands at 320–360 nm and at 360–400 nm.

Containers for test samples should be chemically inert and transparent to light. Companies should either maintain an appropriate temperature control to minimize the potential for local effects due to temperature or include a dark control in the same environment side by side with the test samples (unless otherwise justified). Precautions should be taken to minimize changes in physical state of the samples (e.g., sublimation, evaporation, or melting) and to ensure minimal interference with the exposure of the test samples. Possible interaction between samples and containers or protective materials should be considered and eliminated as much as possible.

The study design for confirmatory testing (see below) should include an overall illumination of not less than 1.2 million lux hours and an integrated near-UV energy exposure of not less than 200 watt hours m^{-2} for drug and formulated product. Samples may be exposed side by side with a validated actinometric system (such as quinine for the near-UV region; the guideline includes two options for calibrated quinine actinometers) or for an appropriate period of time using calibrated radiometers/lux meters.

The results should be evaluated to determine whether acceptable levels of change are induced by light exposure, taking into account other stability data obtained for the drug and the product concerned. Special labeling and packaging may then be identified to ensure that the product will remain within the proposed specifications for the shelf life of the product.

Drug Substance Testing

The test program for drug substance testing should be in two phases: forced degradation and confirmatory test-

ing. In the forced degradation study, the drug may be tested as is or in simple solution or suspension. A variety of (justified) exposure conditions may be applied depending on the photosensitivity of the drug and the intensity of the light sources, but exposure may need to be limited if extensive decomposition occurs and may be terminated if the material is found to be photostable.

These studies are used to establish the overall light sensitivity of the material and may also be used for elucidation of the degradation pathways and validation studies. Under the conditions used for this phase of the study, degradation products may be formed that are unlikely to be formed under the confirmatory test conditions. However, the information may be useful in the development and validation of analytical procedures. If it is demonstrated that these degradation products are not formed in the confirmatory studies, they do not need to be studied further. The initial test is normally conducted on a single batch of material; if the results are equivocal, up to an additional two batches may need to be examined.

Confirmatory tests should be carried out under the conditions listed above to provide necessary information concerning the precautions needed for handling the drug and for its packaging and labeling. The confirmatory test is normally carried out on a single batch of material unless the results are equivocal, which requires an additional two batches to be examined.

Testing samples should be placed in chemically inert and transparent containers. Direct challenge studies of solid drugs may involve a suitable quantity of the substance being placed as a layer not more than 3 mm deep in a glass or suitable plastic dish, protected with a suitable transparent cover if necessary.

Samples should be examined for changes in physical properties (appearance, color of solution, clarity of solution, etc.), assayed, and examined for degradation products. The analytical methods should have been validated for potential photodegradation products and should be capable of resolving and detecting such degradation products, especially those appearing in the confirmatory tests. Sampling of solids should ensure that representative portions are tested. Other materials should also be homogeneous. Protected samples used as dark controls should be analyzed at the same time.

The results from the forced degradation stress tests cannot be expected to establish qualitative or quantitative limits for change, but should be used to develop and validate test methods for use in the confirmatory studies. The confirmatory studies should identify the extent of change that occurs (and the manufacturer then has to decide whether this is acceptable) and will help to identify precautions necessary for the manufacture, formulation, and packaging of the finished product. Results from other formal stability studies should also be taken into account to confirm that the substance will remain within justified limits at the time of use.

Finished Product

Studies of formulated product should follow the sequence indicated above: fully exposed product, product in its primary container (unless the container is impermeable to light, e.g., a metal tube or can), and, if necessary, product in its full marketing packaging. In-use photostability testing may be considered for products such as infusion fluids and dermal products, depending on the instructions for use. Normally, only one batch of product is tested unless the results obtained are equivocal, in which case an additional two batches should be examined.

Samples should be placed in suitable containers, taking into account the physical characteristics of the product and the need to ensure minimal changes of the physical state while ensuring minimal interference with the irradiation of the test samples. The use of cooling or the placement of samples in sealed containers may be justified. Interactions between containers and the like and product should be considered, and any such materials should be eliminated when they are not essential for the conduct of the test.

Product tested outside its primary pack should be placed in chemically inert and transparent containers. Direct challenge studies of solid products may involve a suitable quantity of the material being placed as a layer not more than 3 mm deep in a glass or suitable plastic dish and protection with a suitable transparent cover if necessary. Tablets, capsules, or other forms should be placed in a single layer. If direct exposure is not practical (e.g., due to oxidation), the sample should be placed in a suitable inert container (e.g., made of quartz). Product tested in the primary container should be placed to provide the most uniform exposure (e.g., horizontal or transverse placement), although special adjustments may be needed in the case of large-volume containers.

Samples should be tested after exposure using representative samples (e.g., of 20 capsules or tablets) or other samples (or solutions), ensuring homogeneous distribution. Physical properties (appearance, clarity and color of solution, disintegration or dissolution of capsules, etc.) and chemical properties (assays for the active ingredient and degradation products) should be undertaken. Exposed and dark control samples should be tested at the same time.

Committee for Proprietary Medicinal Products Guideline for Reduced Stability Testing: Bracketing and Matrixing

The CPMP guideline, Reduced Stability Testing Plan—Bracketing and Matrixing, Annex to Note for Guidance on Stability Testing: Stability Testing of New Drug Substances and Products, is an annex to the parent ICH stability guideline and was issued for comment in September 1996 and adopted by the CPMP in October 1997. The concept of reduced testing plans is acceptable only for closely related substances and products such as the same dosage form (comparable specifications), same (or very closely similar) formulation, and the same product using different batches of the same active ingredient. Batch-to-batch variability should be small.

A manufacturer who has used matrix or bracketing studies in developing a product should justify the chosen protocol and show that the proposed shelf life for each product strength and pack is supported using stability data on both the active ingredient and the formulated products.

It is normally expected that three batches of each strength, of each container type, and of each pack size are stability tested at 25°C and 60% RH for 12 months and at 40°C and 75% RH for 6 months (or alternative conditions) as per the main ICH guideline. However, by the use of appropriate bracketing or matrixing studies, the number of samples analyzed at each test point may be substantially reduced yet produce adequate information to justify the proposed shelf life of products concerned. The manufacture and start of analysis may be staggered.

Bracketing or matrixing would normally be acceptable in the following cases:

- strength changes with no or small changes in the proportion of ingredients or achieved by varying the amount of active ingredient and one or two major excipients
- container size changes with the same contact materials
- change to an equivalent closure system
- change to a manufacturing site within the same company
- change of batch size

Matrixing would normally be acceptable in the following cases:

- strength changes associated with significant changes to the proportions of ingredients or changes in one or two minor components
- changes to fill volumes in containers
- introduction of a closure system of nonequivalent performance
- changes to the manufacturing process
- the introduction of manufacturing by a different company

Bracketing

The example in Table 2 is given in the guideline for a product line having three strengths of product with the same relative composition of excipients, two types of packaging, and three pack sizes for one of these types of packaging.

Matrixing

In the matrixing type of protocol, all product strengths, packaging materials, pack sizes, and the like are included and tested to some extent. None of the product variants are excluded from the test program. Examples of the sampling schedules for the first and second time pulls is included in the guideline are given in Tables 3 and 4.

Other statistically based designs may also be used. In all cases, the manufacturer will need to ensure that the distribution of all variables is even during the period of the protocol. Consultation with regulatory agencies may be advisable before employing complex matrix designs.

Initial and final time points should include all samples. The statistical basis of a low testing matrix such as a 1/3 design is better when the protocol covers several strengths and/or pack sizes rather than a product with a single strength and pack size, for example.

The degree of reduction in the testing may be affected by factors such as the stability of the active ingredient and the physical stability of the dosage form. With a very stable drug in a conventional tablet formulation, a 1/3 matrix could be acceptable, but if evidence of significant changes is found during the real-time arm of the stability trial, the testing frequency will need to be increased to (for example) a 2/3 matrix for the remaining part of the study.

Committee for Proprietary Medicinal Products Guideline: Maximum Shelf Life for Sterile Products After First Opening or Following Reconstitution

The CPMP draft guideline on maximum shelf life for sterile products after first opening or following reconstitution was issued for comment in June 1996; a second revised version was released for comment in June 1997;

Table 2

Example of Bracketing Design

	Dosage Strength/Active Substance Lot (A, B, C)								
	50 mg			75 mg			100 mg		
Pack Type	A	B	C	A	B	C	A	B	C
Blister	X	X	X	(X)	(X)	(X)	X	X	X
HDPE/15	X	X	X	(X)	(X)	(X)	X	X	X
HDPE/100	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
HDPE/500	X	X	X	(X)	(X)	(X)	X	X	X

(X) = sample not tested.

Table 3

Matrix Design (First Time Point)

	Dosage Strength/Active Substance Lot (A, B, C)								
	50 mg			75 mg			100 mg		
Pack Type	A	B	C	A	B	C	A	B	C
Blister	1	1	(1)	(1)	1	1	1	(1)	1
HDPE/1	(1)	1	1	1	(1)	1	1	1	(1)
HDPE/2	1	(1)	1	1	1	(1)	(1)	1	1

First time point: for the 1/3 testing matrix, 1 = sample not tested, (1) = sample tested; for the 2/3 testing matrix, 1 = sample tested, (1) = sample not tested.

Table 4

Matrix Design (Second Time Point)

	Dosage Strength/Active Substance Lot (A, B, C)								
	50 mg			75 mg			100 mg		
Pack Type	A	B	C	A	B	C	A	B	C
Blister	1	1	(1)	(1)	1	1	1	(1)	1
	(2)	2	2	2	(2)	2	2	2	(2)
HDPE/1	(1)	1	1	1	(1)	1	1	1	(1)
	2	(2)	2	2	2	(2)	(2)	2	2
HDPE/2	1	(1)	1	1	1	(1)	(1)	1	1
	2	2	(2)	(2)	2	2	2	(2)	2

First and second time points.
Test/no test convention as in note to Table 3.

and a considerably revised third version was adopted in January 1998, with an operational date of July 1998. The guideline applies to all sterile products for human use except radiopharmaceuticals and extemporaneously prepared or modified preparations. It is emphasized that the end user is responsible for maintaining the quality of the product to be administered to patients, but that the manufacturer (authorization holder) should conduct appropriate studies and provide relevant information in the product information. Reference is also made to the European Pharmacopoeial recommendations regarding storage times and conditions of storage for particular categories of sterile products once they have been opened.

The guideline suggests wording to be used for unpreserved sterile products (including injections and intravenous infusions) and for aqueous preserved products and nonaqueous products. The proposals include references to storage time (in hours or days, as appropriate) and conditions (temperature). For injectable products not containing a preservative, it is suggested that the storage time and conditions should not normally be longer than 24 hr at 2° to 8°C unless reconstitution or dilution had taken place in controlled and validated aseptic conditions. For preserved sterile products, it is indicated that usage periods should not normally be more than 28 days.

Committee for Proprietary Medicinal Products Stability Guideline: Abridged Applications (1989 Version)

In the CPMP stability guideline for abridged applications (1989 version), it is indicated that information on the stability of the active ingredient may be determined by experimental studies or by evidence from the scientific literature for known substances (although comparative accelerated studies may need to be considered, for example, when there is a significant change in the route of synthesis from one approved by the regulatory authorities or when there is a significant change to the production method). When multiple sources of the active ingredient are requested, stability data relating to each may be required. Data on a minimum of two batches will be required when such studies are needed.

Studies of the finished product (normally at least three batches unless the product is stable, i.e., no significant degradation products are found, or when the active ingredient has already been used in licensed products) will be required to establish the shelf life specification, the shelf life, and recommended storage conditions. Specific studies will also be required when the product is labile once the container has been opened.

Real-time studies will be required. These should be carried out under a variety of controlled conditions: The properties of the product at temperatures between 20°C and 30°C should be able to be evaluated. The mean kinetic temperature for Europe should be taken as 25°C. A variety of other storage conditions should also be considered, such as below −15°C, from 2°C to 8°C (refrigeration), and freeze-thaw cycling. High humidity may be relevant (i.e., > 75% RH), as may combinations of elevated temperature and humidity (e.g., 40°C/75% RH) and exposure to natural or defined artificial light conditions.

The summarized (tabular or graphical) data should be presented for each batch of product. The results of ongoing studies should be provided as they become available, including the results from the first two or three production batches. These results should be discussed in the Expert Report.

No labeling statement is required if the product is stable at up to 30° unless special storage requirements apply (e.g., do not freeze, do not refrigerate, etc.). In other cases, a recommended temperature storage range should be stated (in °C).

Data will also be required for certain variations, such as when there are major changes to the composition of the product, to packaging materials, or to the method of preparation of the product. Results from comparative accelerated and long-term stability studies would normally be required prior to authorization.

This guideline has been replaced by a newer one, ''Stability Testing of Existing Active Substances and Related Finished Products'' (discussed next).

Committee for Proprietory Medicinal Products Guideline: Stability Testing of Existing Active Substances and Related Finished Products

The CPMP guideline regarding Stability Testing of Existing Active Substances and Related Finished Products was released for comment in March 1997 and was adopted by the CPMP in April 1998. It came into effect in October 1998.

It is intended that this guideline applies to chemically active substances that have been previously approved in the EU and to products containing them, but not to radiopharmaceuticals or biological/biotechnological products. The test conditions in the guideline refer to the parent ICH guideline on stability testing of new active substances and products containing them. A systematic approach to the presentation and interpretation of data is encouraged.

Active Ingredients

Data from stress testing and formal studies may be expected. The extent of data requirements will depend on the status of the active ingredient concerning the availability of relevant (i.e., European) monographs, published data, and the like.

When a pharmacopoeial monograph is available and includes data under the headings ''purity test'' and/or ''transparency statement'' for named degradation products or when additional information on the degradation pathways is available in the published scientific literature, no stress testing will be required. Such data should be generated in other circumstances.

When a pharmacopoeial monograph is available that includes suitable degradation product limits (but no definition of a retest interval), it would be open to the applicant to state that the material complies with the monograph immediately prior to use in the manufacture of the finished product. In this case, no stability data would be required, provided that the suitability of the pharmacopoeial monograph has been established for the particular named ingredient source. Alternatively, the retest interval could be set based on results from long-term stability tests.

When data are required, the following general suggestions are included in the guideline concerning the selection of batches for testing, although alternative test conditions can be proposed and justified:

- Option 1: Two industrial-scale batches made using the same synthetic route and in the same packaging used for storage and distribution or one batch simulating that packaging at the time of submission (accelerated and long-term study data) and a further batch (placed in a long-term test) to the same protocol after approval. Accelerated test conditions are 40°C ± 2°C, 75% RH ± 5% RH; 6 months of data. Long-term test conditions are 25°C ± 2°C, 60% RH ± 5% RH; 6 months of data.
- Option 2: At least three pilot-scale batches using the same synthetic route at the time of submission (6 months of accelerated and 12 months of long-term study data) and extended to cover the retest period and in the appropriate packaging, with the first three production-scale batches manufactured post-approval placed in a long-term test to the same protocol, with results being submitted as they become available.

Results from studies should be submitted to the regulatory authorities when available.

In both cases, the testing intervals should be according to the main ICH guideline. Intermediate testing conditions can be used when significant changes occur under accelerated conditions. For temperature-sensitive materials, long-term testing should be performed at 5°C ± 3°C with the relative humidity conditions reported, and accelerated studies should be undertaken at 25°C ± 2°C and 60% RH ± 5% RH for 12 and 6 months. The usual requirements for validated analytical methods, collection of data on features susceptible to change and having a potential impact on quality safety or efficacy, and so on apply.

The specification should include limits of acceptability. This should include individual and total upper limits for impurities, including degradation products. The limits should be based on safety and efficacy considerations.

Labeling statements for active ingredients should indicate appropriate conditions based on the stability evaluation, but should avoid terms such as ''ambient conditions'' or ''room temperature.''

Finished Product

At the time the application for authorization is submitted, data will normally be expected from accelerated (6 months of data at 40°C ± 2°C/60% RH ± 5% RH) and long-term studies of the proposed formulation and dosage form intended for marketing. For conventional dosage forms such as immediate-release solid dosage forms and solutions and when the active substances are known to be stable (i.e., remains within initial specifications after 2 years at 25°C/60% RH and after 6 months at 40°C/75% RH), long-term data from at least two pilot-scale batches for 6 months at 25°C ± 2°C/60% RH ± 5% RH will normally be accepted. In other cases (e.g., prolonged-release dosage forms or when the active substance is known to be unstable), stability data are likely to be required for three batches, two at pilot scale and a third smaller batch, for 12 months at the same conditions. Other storage conditions may be justified, for example, if there is ''significant change'' under the normal conditions. The permitted conditions in special cases (e.g., products stored under refrigerated conditions or liquid products in semipermeable containers) follow the advice given in the parent ICH guideline. The usual pattern of test sampling points should be followed.

In all cases, the manufacturing method should be a simulation of that to be applied to large-scale marketing batches, and the packaging used should be the same as that used for the commercial product.

The methods should investigate preservative losses, physical property changes, and, when necessary, micro-

biological attributes, as well as chemical and biological stability. Preservative efficacy tests, as well as preservative assays, should be undertaken on stored samples, particularly when different limits are proposed for preservatives in the release and shelf life specifications. In the case of particle size and/or dissolution rate specifications, reference should be made to batches used to establish bioavailability or bioequivalence.

Specifications should be proposed for shelf life and for release (when the values differ from the shelf life specification values). The shelf life specifications, including specific upper limits for degradation products (based on efficacy and safety considerations), may deviate from the release limits provided that these are justified by the changes observed in storage.

The data should be analyzed statistically to establish the degree of variability between batches (as per the parent ICH guideline) unless there is so little variability that it is apparent that the requested shelf life will be granted.

In establishing the acceptable shelf life, limited extrapolation of the available real-time data may be allowed, particularly when the accelerated data are supportive. However, since this assumes that the degradation mechanism will continue to apply beyond the observed data points, it is important to consider what is known about the degradation mechanism and the goodness of fit of the data to any mathematical model and any other supportive data, including mass balance. It is indicated that the normal extrapolation is twice the length of the real-time studies (but not more than 3 years).

Based on the available data, appropriate storage and labeling statements should be proposed. These should refer, as appropriate, to conditions such as temperature (avoiding the terms ''ambient conditions'' and ''room temperature''), light, and humidity.

Committee for Veterinary Medicinal Products Guideline: In Use Stability Testing of Veterinary Medicinal Products (Excluding Immunological Veterinary Medicinal Products)

The guideline for In Use Stability Testing of Veterinary Medicinal Products (Excluding Immunological Veterinary Medicinal Products) was adopted by the Committee for Veterinary Medicinal Products (CVMP) in March 1996 and came into force in September 1996. While it is primarily addressed to veterinary products other than immunologicals, it may also be applied to (or this type of data may be requested for) human products by regulatory agencies. The CPMP does not appear to intend to develop its own guideline on this topic. The test procedure involves removal of aliquots of the (reconstituted if appropriate) product from the container at regular intervals over the proposed in-use shelf life.

The guideline is intended to offer information for the design of studies to establish the period for which a multiuse product may be used after the first dose has been removed from the container without the integrity of the product being adversely affected. Such testing is required for all parenteral products in multidose containers, and particularly so if the headspace in the vial is replaced by an inert atmosphere during manufacture. Multidose oral or topical dosage forms should be tested if a specific stability-related problem has been identified once the container has been opened. Oral products may also need to be tested (e.g., when the active ingredient was subjected to oxidative degradation and was packed in a well-filled oxygen-impermeable container).

At least two batches of product (of stated batch number and batch size; production-scale lots are preferred, although representative development-scale batches will be accepted) in the proposed marketing container-closure system should be tested. At least one of those batches should be approaching the end of its shelf life in the case of products that have chemical characteristics that will alter significantly during the shelf life (e.g., antioxidant levels). When different package sizes will be marketed, the one offering the greatest demand on the system should be used.

The test should simulate as much as possible the intended use of the product. At appropriate intervals, aliquots of the product should be withdrawn by the usual technique, with the product being stored under the recommended conditions throughout the test period. In some cases, it may be appropriate to remove a significant proportion of the contents at the start of the test only and then to reexamine the product up to the end of its proposed in-use shelf life; or, it may be more relevant to remove aliquots on a daily basis if this is more representative of the normal use pattern for the product. More than one test may be necessary if a product may be used in different ways. In any case, the rationale for the design adopted should be explained.

Chemical (active ingredient assays, antimicrobial and chemical preservative content, degradation products), physical (pH, color, clarity, closure integrity, particulate contamination, particle size), and microbiological properties (total viable count, antimicrobial preservative efficacy, single or repeat challenge) of the product should

be monitored during the study. Test procedures should be described and validated. The results should be summarized and tabulated. Conclusions should be made, drawing attention to any anomalous results.

The in-use shelf life and any advice on discarding the product should be included in the summary of product characteristics. Suitable labeling should be applied—including a space in which the user can write in the date when the first dose of product is withdrawn from the container. The in-use shelf life should also be stated on the label if space permits.

Committee for Proprietary Medicinal Products and Committee for Veterinary Medicinal Products Guideline: Inclusion of Antioxidants and Antimicrobial Preservatives in Medicinal Products

The CPMP and CVMP guideline for the inclusion of antioxidants and antimicrobial preservatives in medicinal products was released for comment in July 1996 and adopted in July 1997, and had an operational date of January 1998. With respect to stability studies, it is suggested that the guideline on stability of new dosage forms should be followed. Antioxidant and antimicrobial preservative levels should be quantified periodically throughout the shelf life of the finished product, and preservative efficacy should be established using the European Pharmacopoeial methodology both at the end of shelf life and at the lower end of the proposed preservative content.

Products intended for use on more than one occasion should also be tested for preservative efficacy under simulated in-use conditions. It might also be necessary to investigate preservative efficacy following storage of opened or used containers during the proposed in-use shelf life.

Draft Committee for Proprietary Medicinal Products Guideline: Dry Powder Inhalers

The CPMP guideline concerning dry powder inhalers was released for comment in October 1997 and adopted in June 1998, and had an operational date of December 1998. It is suggested that dose, dose delivery, and particle characteristics of these products need to be shown over the proposed shelf life and over the proposed period of use. Active ingredient assays and determinations of related substances will be expected. The particular significance of exposure to moisture is emphasized in the guideline, with suggested testing conditions of 25°C/60% RH and 40°C/75% RH. No special storage instructions relating to moisture exposure are likely to be required if the product complies with its shelf life specification after exposure to such conditions. The exception to this is when an overwrap is used for the product, but the unwrapped product was unable to withstand the suggested stability test conditions for a period of, say, 3 to 6 months (to simulate normal use of the product).

Committee for Proprietary Medicinal Products Guideline: Declaration of Storage Conditions for Medicinal Products in the Product Particulars

The CPMP guideline concerning declaration of storage conditions for medicinal products in the product particulars was circulated for comment in June 1997, adopted in January 1998, and came into effect in June 1998. The guideline defines, based on the stability results, the types of statement to be included in the summary of product characteristics and the product labeling and leaflet. It is intended that the wording in the guideline be used verbatim, although additional or alternative storage statements will be allowed when necessary to protect the product, but these statements will need to be supported with data. Any alternative storage recommendation must be achievable in practice. The use of the terms ''room temperature'' and ''ambient conditions'' is stated to be unacceptable.

When a product is stable at 25°C/60% RH and 40°C/75% RH, no labeling statement is required, but ''Do not refrigerate or freeze'' may be added. When products are stable at 25°C/60% RH and 30°C/60% RH, the labeling should state ''Do not store above 30°C'' and may state ''Do not refrigerate or freeze.'' Products stable at 25°C/60% RH should state ''Do not store above 25°C'' and may state ''Do not refrigerate or freeze.'' For products stable at 5°C, the label should state ''Store at 2°C–8°C'' and may state ''Do not freeze.'' Products that are stable below 0°C should state ''Store in a freezer'' and state a justified temperature.

With regard to statements relating to protection from moisture or light, it is indicated that the inclusion of warning statements should not be an alternative to the correct choice of container in the first place. However, the following statements may be allowed: regarding moisture sensitivity, ''Keep the container tightly closed'' (for plastic bottles, etc.) or ''Store in the original package'' (for blisters); and regarding light sensitivity, ''Store in the

original container'' or ''Keep container in the outer carton.''

European Union Requirements for Variations (Changes) Related to Stability

In the European Union, Commission Regulation 541/95 introduced a procedure for classification and assessment of applications to vary marketing authorizations, including those related to stability. This was amended by Commission Regulation 1146/98, which came into effect in June 1998. These measures introduced the concept of classifying variations into three classes: minor, or type I (with a ''notification'' procedure); major, or type II (with an assessment and approval procedure); and those with changes that were so significant that they required a new marketing authorization application. The simplified type I procedure could be applied in cases for which (*a*) the requested changes are supported by data generated according to the originally approved protocol and that show that the originally agreed specifications are still met, and (*b*) that the maximum requested shelf life is not more than 5 years, and that consequential changes to the product information form part of the application for a variation. Examples of such variations are discussed below.

Changes that do not meet these requirements will be subjected to the type II variation procedure, which includes a longer processing time and requires positive approval prior to implementation.

The main types of application with stability-related changes that are identified in the regulations as being type I (and the conditions that have to be met) are the following:

20. *Extensions to the shelf life as foreseen at the time of authorization*. Conditions to be fulfilled: Stability studies have been done according to the protocol that was approved at the time of the issue of the marketing authorization; the studies must show that the agreed end of shelf life specifications are still met; the shelf life does not exceed 5 years.

20A. *Extension to the shelf life/retest period of the active substance*. Condition to be fulfilled: Stability studies must show that the agreed specifications are still met.

21. *Change in the shelf life after first opening*. Condition to be fulfilled: Studies must show that the agreed end of shelf life specifications are still met.

22. *Change in the shelf life after reconstitution*. Condition to be fulfilled: Studies must show that the agreed end of shelf life specifications are still met for the reconstituted product.

23. *Change in storage conditions*. Condition to be fulfilled: Stability studies have been done according to the protocol that was approved at the time of issue of the marketing authorization. The studies must show that the agreed end of shelf life specifications are still met.

Stability data will be expected for form part of the supporting package for variations for excipient replacement (provided that the replacement is for a material with comparable characteristics, except for vaccines and immunological products, for which a new application may be required), for coating changes on solid dosage forms (for which dissolution characteristics should be unchanged), and for changes to the container and closure system. See below for further discussion.

Other variations concerned directly with shelf life and in-use life of pharmaceuticals are likely to be type II variations, such as those that do not comply with the conditions to be fulfilled listed above.

The CPMP adopted a guideline on stability studies for type II variations in April 1998, and this had an operational date of October 1998. It is indicated that the guidance is intended to provide general information, but that it is intended to allow sufficient flexibility to allow for different practical situations that may be encountered (although alternative approaches should be scientifically justified).

The guideline points out that stability studies should be continued to the approved retest interval for active substances and shelf life for products, and that the regulatory authorities should be advised of any problems that are identified. The specific examples covered in the document include changes to the manufacturing process for the active substance, a change in composition of the finished product, or a change in the immediate packaging of the finished product.

In all cases, the relevant available information on the stability of the active substance (stability profile, including stress test results, supportive data, and primary accelerated and long-term testing data) and finished product (primary data from accelerated and long-term studies and any supportive data) should be taken into account. Appropriate additional studies will then need to be reported.

The data requirements at the time of submission of the variation will depend on the particular circumstances. The applicant should investigate whether the proposed

change(s) have a potential impact on the quality characteristics of the active substance and/or the product. Examples are discussed below. In addition, the first three production batches made postapproval should be placed in long-term and accelerated stability studies using the same protocols as used for the submitted data. Data should be submitted to the authorities when available. Normal extrapolation of the data will be allowed (e.g., up to two times the real-time data up to a limit of 3 years).

Changes to the Manufacturing Process for the Active Substance

Modification(s) to One or More Steps of the Same Route of Synthesis

When the physical characteristics, impurity profile, or other quality characteristics of the active substance are adversely affected by the change, there will be a need to provide 3 months of comparative accelerated and long-term data on one batch of product at not less than pilot scale for stable drugs. In other cases, 6 months of data will be required from three pilot-scale batches.

When the change is to the final stage of synthesis (e.g., new solvent or new crystallization method), additional accelerated and long-term data (3 months, two pilot-scale batches) may be needed for solid dosage forms, for which the physical characteristics may have an impact on the stability of the product.

Change of Synthetic Route

Comparative accelerated and long-term data will be required on three batches of at least pilot-scale manufacture for 6 months.

When there is a change of active substance specification that might affect the finished product (e.g., physical characteristics, degradation product levels), data may also be required on the finished product using at least two pilot-scale batches and reporting 3 months of data at the time of submission.

Changes to the Composition of the Finished Product

For conventional dosage forms such as conventional release solid dosage forms and solutions in which the active substance is stable, there will be a requirement for 6 months of data to be supplied from two pilot-scale batches from long-term and accelerated conditions. For critical dosage forms and less stable active substances, 6 months of data from three batches of product under long-term and accelerated conditions will be required.

Changes to the Immediate Packaging of the Finished Product

When a less protective package is introduced or there is a risk of interaction (e.g., with liquid or semiliquid products), 6 months of data will be required from long-term and accelerated studies of three pilot-scale batches of the product.

World Health Organization Stability Guidelines

While the WHO guidelines for stability testing are not directly applicable in the ICH regions, a summary of their requirements is included in the Appendix to this paper. It seems probable that some account will be taken of these during the revision of the main ICH guideline.

DISCUSSION

The European regulatory agencies have adopted the ICH guidelines for stability testing, although the practical implementation may differ in detail from that applied in the other ICH regions. However, there is a wide range of other relevant guidelines—generated either by the ICH or by the CPMP—that add to the statutory requirements included in the EU Directives and Regulations affecting pharmaceutical products, particularly Directives 65/65/EEC and 75/318/EEC as amended by 91/507/EEC.

This paper has attempted to bring together and summarize many of the requirements and proposals included in guidance documents that affect the types of stability data required for new chemical active substances and products containing them and for existing chemical active substances and products containing them.

GLOSSARY

The terms in this listing are taken from ICH guidelines unless otherwise indicated.

Accelerated testing
Studies designed to increase the rate of chemical degradation or physical change of an active substance or drug product by using exaggerated storage conditions as part of the formal, definitive, storage programme. These data, in addition to the long term stability studies, may also

be used to assess longer term chemical effects at non-accelerated conditions and to evaluate the impact of short term excursions outside the label storage conditions such as might occur during shipping. Results from accelerated testing studies are not always predictive of physical change.
WHO definition similar: Accelerated stability testing.

Active substance; Active ingredient; Drug substance; Medicinal substance
The unformulated drug substances which may be subsequently formulated with excipients to produce the drug product.

Bracketing
The design of a stability schedule so that at any time point only the samples on the extremes, for example of container size and/or dosage strengths, are tested. The design assumes that the stability of the intermediate condition samples are represented by those at the extremes.
[Where a range of dosage strengths is to be tested, bracketing designs may be particularly applicable if the strengths are very closely related in composition (eg for a tablet range made with different compression weights of a similar basic granulation, or a capsule range made by filling different plug fill weights of the same basic composition into different size capsule shells). Where a range of sizes of intermediate containers are to be evaluated, bracketing designs may be applicable if the material of composition of the container and the type of closure are the same throughout the range.]

Climatic zones
The concept of dividing the world into four zones based on defining the prevalent annual climatic conditions.
[See the table at the end of this section]
WHO definition similar

Confirmatory studies [Photostability testing]
Those [studies] undertaken to establish photostability characteristics under standardised conditions. These studies are used to identify precautionary measures needed in manufacturing or formulation and whether light resistant packaging and/or special labelling is needed to mitigate exposure to light.

Dosage form; Preparation
A pharmaceutical product type, for example tablet, capsule, solution, cream, etc, that contains a drug ingredient generally, but not necessarily, in association with excipients.

Drug product; Finished product
The dosage form in the final immediate packaging intended for marketing.

Excipient
Anything other than the drug substance in the dosage form.

Expiry; Expiration date
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 must not be used.
WHO definition:
The expiry date given on the individual container (usually on the label) of a drug product, designates the date up to and including which the product is expected to remain within specifications, if stored correctly. It is established for every batch by adding the shelf life to the manufacturing date.

Forced degradation studies
Those studies undertaken to degrade the sample deliberately. These studies, which may be undertaken in the development phase normally on the drug substance, are used to evaluate the overall photosensitivity of the material for method development purposes and/or degradation pathway elucidation.

Formal (systematic) studies
Stability evaluation of the physical, chemical, biological, and microbiological characteristics of a drug product and a drug substance, covering the expected duration of the shelf life and re-test period, which are claimed in the submission and which will appear in the labelling.

Immediate (primary) pack
That constituent of the packaging that is in direct contact with the drug substance or drug product, and includes any appropriate label.

Marketing pack
The combination of immediate pack and other secondary packaging such as a carton.

Mass balance; Material balance
The process of adding together the assay values and levels of degradation products to see how closely these add up to 100 per cent of the initial value, with due consideration of the margin of analytical precision.
This concept is a useful scientific guide for evaluating data but it is not achievable in all circumstances. The focus may instead be on assuring the specificity of the assay, the completeness of the investigation of routes of degradation, and the use, if necessary, of identified degradants as indicators of the extent of degradation via particular mechanisms.

Matrixing
The statistical design of a stability schedule so that only a fraction of the total number of samples are tested at any specified sampling point. At a subsequent sampling point, different sets of samples of the total number would be tested. The design assumes that the stability of samples tested represents the stability of all samples.
[The differences in the samples for the same drug product should be identified as, for example, covering different batches, different strengths, different sizes of the same container and closure and possibly in some cases different container/closure systems.
Matrixing can cover reduced testing when more than one variable is being evaluated. Thus the design of the matrix will be dictated by the factors needing to be covered and evaluated. This potential complexity precludes inclusion of specific details and examples, and it may be desirable to discuss design in advance with the Regulatory Authority, where this is possible. In every case it is essential that all batches are tested initially and at the end of the long term testing.]

Mean kinetic temperature
When establishing the mean values of the temperature, the formula of J D Haynes (*J Pharm Sci*, **60,** 927-929, 1971) can be used to calculate the mean kinetic temperature. It is higher than the arithmetic mean temperature and takes into account the Arrhenius equation from which Hayes derived his formula.
WHO definition:
The single test temperature corresponding to the effects on chemical reaction kinetics of a temperature-time distribution of each of the four world climatic zones and according to the formula developed by Haynes J D, Journal of Pharmaceutical Sciences, *1971, **60:** 927-929. It is a higher value than that of the arithmetic mean temperature.*

New molecular entity; New drug substance
A substance which has not previously been registered as a new drug substance with the national or regional authority concerned.

Pilot plant scale
The manufacture of either drug substance or drug product by a procedure fully representative of and simulating that to be applied on a full manufacturing scale. For oral solid dosage forms this is generally taken to be at a minimum scale of one tenth of full production or 100000 tablets or capsules, whichever is the larger.

Primary stability data
Data on the drug substance stored in the proposed packaging under storage conditions that support the proposed re-test date.

Data on the drug product stored in the proposed container-closure for marketing under storage conditions that support the proposed shelf life.

WHO definition:
Real time (long term) stability studies
Evaluation of experiments for physical, chemical, biological, biopharmaceutical and microbiological characteristics of a drug, during and beyond the expected time of shelf-life and storage of samples at expected storage conditions in the intended market. The results used to establish shelf-life, to confirm projected shelf-life and recommend storage conditions.

Re-test date
The date when samples of the drug substance should be re-examined to ensure that material is still suitable for use.

Re-test period
The period of time during which the drug substance can be considered to remain within the specification and therefore acceptable for use in the manufacture of a given drug product, provided that it has been stored under the defined conditions; after this period, the batch should be retested for compliance with specification and then used immediately.

Shelf-life; Expiration dating period
The time interval that a drug product is expected to remain within the approved shelf-life specification provided that it is stored under the conditions defined on the label in the proposed containers and closure.
WHO definition:
The period of time during which a pharmaceutical product is expected, if stored correctly, to comply with the specification ['shelf life specification: ie requirements to be met throughout the shelf-life of the drug product (should not be confused with 'release specification')] as determined by stability studies on a number of batches of the product. The shelf-life is used to establish the expiry date of each batch.

Specification—check/shelf life
The combination of physical, chemical, biological and microbiological test requirements that drug substance must meet up to its re-test date or a drug product must meet throughout its shelf life.

Specification—release
The combination of physical, chemical, biological and microbiological test requirements that determine a drug product is suitable for release at the time of its manufacture.

WHO definition
Stability
The ability of a pharmaceutical product to retain its properties within specified limits throughout its shelf-life. The following aspects of stability are to be considered: chemical, physical, microbiological and biopharmaceutical.

WHO definition
Stability tests
Stability tests are a series of tests designed to obtain information on the stability of a pharmaceutical product in order to define its shelf-life and utilisation period under specified packaging and storage conditions.

Storage conditions tolerances
The acceptable variation in temperature and relative humidity of storage facilities. The equipment must be capable of controlling temperature to within a range of ± 2°C and Relative Humidity to ± 5%. The actual temperatures and humidities should be monitored during stability storage. Short term spikes due to opening of doors of the storage facility are accepted as unavoidable. The effect of excursions due to equipment failure should be addressed by the applicant and reported if judged to impact stability results. Excursions that exceed these ranges (ie ± 2°C and/or ± 5% RH) for more than 24 hours should be described in the study report and their impact assessed.

Stress testing (drug product)
Light testing should be an integral part of stress testing. Special test conditions for specific products (eg metered dose inhalations and creams and emulsions) may require additional stress testing.

Stress testing (drug substance)
These studies are undertaken to elucidate intrinsic stability characteristics. Such testing is part of the development strategy and is normally carried out under more severe conditions than those used for accelerated tests.
Stress testing is conducted to provide data on forced decomposition products and decomposition mechanisms for the drug substance. The severe conditions that may be encountered during distribution can be covered by stress testing of definitive batches of the drug substance.
These studies should establish the inherent stability characteristics of the molecule, such as the degradation pathways, and lead to identification of degradation products and hence support the suitability of the proposed analytical procedures. The detailed nature of the studies will depend on the individual drug substance and type of drug product.
This testing is likely to be carried out on a single batch of material and to include the effect of temperatures in 10°C increments above the accelerated temperature test conditions (eg 50°C, 60°C, etc); humidity where appropriate (eg 75% or greater); oxidation and photolysis on the drug substance plus its susceptibility to hydrolysis across a wide range of pH values when in solution or suspension.
Results from these studies will form an integral part of the information provided to the regulatory authorities.
Light testing should be an integral part of stress testing. It is recognised that some degradation pathways can be complex and that under forcing conditions decomposition products may be observed which are unlikely to be formed under accelerated and long term testing. This information may be useful in developing and validating suitable analytical methods, but it may not always be necessary to examine specifically for all degradation products, if it has been demonstrated that in practice these are not found.

Supporting stability data
Data other than primary stability data, such as stability data on early synthetic route batches of drug substance, small scale batches of materials, investigational formulations not proposed for marketing, related formulations, product presented in containers and/or closures other than those proposed for marketing, information regarding test results on containers, and other scientific rationale that support the analytical procedures, the proposed retest period or shelf life and storage conditions.
WHO definition:
Supplementary data, such as stability data on small scale batches, related formulations, products presented in containers other than those proposed for marketing and other scientific rationale that support the analytical procedures, the proposed re-test period or shelf-life and storage conditions.

WHO definition
Utilisation period
A period of time during which a reconstituted preparation or the finished dosage form in an opened multidose container can be used.

APPENDIX

Provisional World Health Organization Guidelines on Stability Testing of Pharmaceutical Products Containing Well-Established Drug Substances in Conventional Dosage Forms

A provisional guideline on the stability testing of well-established drug substances in conventional dosage forms was adopted at a meeting of the Expert Committee

Table A1

Uses of Stability Studies

Phase/Purpose	Accelerated Studies	Real-Time Studies
Development: selection of adequate formulations and container-closure systems	X	
Development and dossier: determination of shelf life and storage conditions	X	X
Dossier: substantiation of claimed shelf life		X
Quality assurance, quality control: verification that no changes have been introduced into the formulation or manufacturing process that can adversely affect the stability of the product	X	X

on Specifications for Pharmaceutical Preparations in November/December 1994.

For products of this type, data are often available in the literature on the decomposition processes and degradation of active substances (e.g., in the unpublished report, WHO/PHARM/86.529) together with adequate analytical methods. In such cases, attention may be concentrated on the stability of the dosage form. Stability of formulated products should be adequately investigated during development of the product, including consideration of the possibility of interactions between the drug substance and excipients and container system components. Due consideration should be given to transport and storage conditions and to the climatic conditions of the places where the product is to be marketed. Appropriate storage recommendations may be needed to ensure compliance with the shelf life proposed for the product as indicated by the labeled expiry date.

The WHO guideline includes definitions of accelerated stability testing, batch, climatic zones, expiry date, mean kinetic temperature, real-time (long-term) stability studies, shelf life, stability, stability tests, supporting stability data, and utilization period.

The purposes of stability testing are identified in Table A1.

The importance of climatic zone is emphasized in the WHO guideline, and additional data are included in the document compared with the CPMP guideline. A summary of the information is included in Table A2.

The recommendation in the WHO document is for products intended for a global market to be tested under the climatic zone IV conditions, that is, real-time studies under conditions as close as possible to those that will be encountered during storage in the distribution system (with a minimum of 12 months of data being submitted with the application) and accelerated testing at 40°C ± 2°C and 75% RH ± 5% RH for 6 months, although other conditions may be used (e.g., 3 months at 45°C–50°C and 75% RH).

In the case of zone II conditions, accelerated conditions of 40°C ± 2°C and 75% RH ± 5% RH for 3 months or 6 months are recommended in the case of a less stable drug substance or for those products for which a limited amount of data is available. When these conditions are not appropriate, alternative conditions may be used, provided that accelerated studies are undertaken at not less than 15°C above the expected long-term storage temperature and relevant humidity conditions.

In addition to the indicated temperature and humidity conditions, it is also suggested that stability studies for liquid products should consider the use of low temperatures (e.g., below 0°C, −10°C to −20°C) freeze-thaw cycles, and refrigeration conditions (2°C to 8°C). Light exposure may also be relevant for some products. Publicly available information on stability of drugs should be taken into account when designing studies.

Intermediate test conditions (e.g., 30°C ± 2°C and 60% RH ± 5% RH) may be used if significant changes occur (e.g., 5% loss of initial potency value; any degradation product exceeding its specification limits; dissolution test failure; fail to meet requirements for physical properties or appearance) in the accelerated studies, with 6 months of data from a 1-year study being submitted with the application.

Three batches of product should be tested except when the active ingredient is known to be fairly stable. The batches should be representative of the manufacturing process and be made at pilot scale or full scale. When possible, different batches of active ingredient should be used to manufacture the stability lots. In addition, production batches should also be tested (e.g., for stable for-

Table A2

Climatic Conditions Data (WHO)

Climatic Zone	Measured Data: Open Air	Measured Data: Storage Room	Calculated Data	Derived Data
I				
Temperature	10.9°C	18.7°C	20.0°C	21°C
Relative humidity	75%	45%	42%	45%
II				
Temperature	17.0°C	18.7°C	21.6°C	25°C
Relative humidity	70%	52%	52%	60%
III				
Temperature	24.4°C	26.0°C	26.4°C	30°C
Relative humidity	39%	54%	35%	35%
IV				
Temperature	26.5°C	28.4°C	26.7°C	30°C
Relative humidity	77%	70%	76%	70%

Note: References to the derivation of these figures are included in the WHO document.

mulations, one batch every other year; for products for which the stability profile has been established, one batch every 3 to 5 years unless a major change has been made to the product, e.g., to the formula or to the method of manufacture). Details of the batches used in the stability trials should be stated: batch number, date of manufacture, batch size, packaging, and so on.

The suggesting sampling program for new products is (*a*) real-time studies, 0, 6, 12, 24, 36 months (or more); (*b*) accelerated studies, 0, 1, 2, 3, (6) months (or more); except when the active ingredient is less stable or when limited data are available (when sampling every 3 months would be appropriate) in the first year, followed by sampling every 6 months in the second year and annually thereafter. For ongoing studies to support a provisional shelf life, the study may be based on sampling every 6 months; for highly stable formulations, annual testing may be sufficient.

Analytical methods should be validated, and assays should be stability indicative. Methods used to quantify degradation products or related substances should be specific and of adequate sensitivity. Suitable methods should be applied to ensure that excipients remain effective and unchanged during the proposed shelf life. The use of a checklist to identify stability characteristics is suggested in the guideline.

A stable product is one that shows no significant degradation or changes in its physical, chemical, microbiological, and biological properties, with the product remaining within its specification.

It is suggested that the stability results should be presented in a tabular or graphical format, with details of the initial and other data points for each batch of product. A standard format is suggested as an example (see Table A3).

The study report should include information on the study design, the results, and the conclusions. The stability evaluation and the derived recommended storage conditions and shelf life relate to a particular formulation and method of production. Some extrapolation from the real-time data—when supported by accelerated data—may be appropriate.

A tentative shelf life of 24 months may be proposed based on

- a stable active ingredient;
- no significant changes in a controlled stability study;
- similar formulations having been assigned a 24-month shelf life;
- a claimed shelf life of not more than twice the period for which real-time data are submitted; and
- an undertaking on the part of the manufacturer to continue real-time stability studies until the proposed shelf life has been covered.

The labeling that may be accepted may be based on

- storage under ‘‘normal conditions,’’ defined by WHO as ‘‘Storage in dry, well-ventilated premises

Table A3

Suggested Format for Stability Test Summary Sheet (WHO)

Accelerated/real-time studies

Name of drug product: _____

Manufacturer: _____

Address: _____

Active ingredient (INN): _____

Dosage form: _____

Packaging: _____

	Batch number	*Date of manufacture*	*Expiry date*
1			
2			
3			

Shelf life: _____ years _____ months

	Batch size	*Type of batch (experimental, pilot plant, production)*
1		
2		
3		

Samples tested (per batch): _____

Storage/test conditions

Temperature _____°C _____ Humidity _____ %RH

Light _____ [lux hours] Pressure _____ [bar]

RESULTS

1. Chemical findings: _____
2. Microbiological and biological findings: _____
3. Physical findings: _____
4. Conclusions: _____

Responsible officer: _____ Date: _____

at temperatures of 15°C–25°C or, depending on climatic conditions, up to 30°C. Extraneous odours, contamination, and intense light have to be excluded,'' although alternative normal conditions may be defined locally having regard to prevalent conditions;
- storage between 2°C and 8°C under refrigeration, no freezing;
- store below 8°C under refrigeration;
- store in a freezer at −5°C to −20°C;
- store below −18°C in a deep freezer.

Additional statements such as ''protect from light'' or ''store in a dry place'' may be used (but not to cover up stability problems).

Appropriate information may also be given for use and storage periods after the product is opened, diluted, or the like.

Relevant European Union Legislative Requirements and Guidelines Relating to Stability Testing

The documents listed here can be found in *The Rules Governing Medicinal Products in the European Union* (published by the Commission of the European Communities) or are available through the following Internet addresses: http:/dg3.eudra.org/eudralex or http:/www.eudra.org (CPMP home page at the EMEA site).

Legislation

Commission Regulation 541/95 of March 10, 1995, concerning the examination of variations of the terms of a marketing authorization granted by a competent authority of a member state, as amended by Commission Regulation 1146/98

Council Directive 65/65/EEC of January 26, 1965, on the approximation of provisions laid down by law, regulation, or administrative action relating to medicinal products.

Council Directive 75/318/EEC of May 20, 1975, on the approximation of the laws of the member states relating to analytical, pharmacotoxicological, and clinical standards, and protocols in respect of the testing of medicinal products

Quality Guidelines

Development Pharmaceutics

Validation of Analytical Procedures: Methodology

Stability Testing of New Active Substances and Medicinal Products

Stability Testing of Active Ingredients and Finished Products

Stability Testing: Requirements for New Dosage Forms

Photostability Testing of New Active Substances and Medicinal Products

Inclusion of Antioxidants and Antimicrobial Preservatives in Medicinal Products

Impurities in New Active Substances

Impurities in New Medicinal Products

Reduced Stability Testing Plan—Bracketing and Matrixing, Annex to Note for Guidance on Stability Testing: Stability Testing of New Drug Substances and Products

Declaration of Storage Conditions for Medicinal Products in the Product Particulars, Annex to Note for Guidance on Stability Testing of New Active Substances; Annex to Note for Guidance on Stability Testing of Existing Active Substances and Related Finished Products

Maximum Shelf Life for Sterile Products for Human Use After First Opening or Following Reconstitution

Stability Testing of Existing Active Substances and Related Finished Products

Stability Testing for a Type II Variation to a Marketing Authorization

Dry Powder Inhalers

REFERENCE

1. Committee for Proprietary Medicinal Products, European Commission, *The Rules Governing Medicinal Products in the European Union, Vol. 3, Guidelines: Medicinal Products for Human Use, Part A, Quality and Biotechnology*, European Commission, 1998, p. 129.