Draft Guidelines on Stability Testing of Drug Substances and Products

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DRAFT GUIDELINE

STABILITY TESTING OF EXISTING DRUG SUBSTANCES AND PRODUCTS

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This third draft has been prepared considering the critical comments from worthy members of IDMA-APA Working Group on Indian Drug Stability Guideline and incorporates fine points discussed at the Colloquium held on the subject at Mumbai on 11.04.2002.

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1. INTRODUCTION

1.1 PURPOSE

This guideline is modelled parallel to the ICH guideline 'Stability Testing of New Drug Substances and Products1 and encompasses essentials from WHO guideline2 and other International guidelines on the subject. It sets out the stability information required in submissions for existing drug substances and associated products and/or to support the claimed shelf life and storage conditions given on the marketed pack.

Note: Alternate approaches to the principles and practices described in this guideline may be acceptable provided they are supported by adequate scientific justification. However, it is desired that significant variations be discussed with competent authorities in advance to avoid rejection or withdrawal of the submission.

1.2 BACKGROUND

Globally, a lot of attention has been paid on outlining the scientific principles and on the development of the International/national and harmonized guidelines on stability testing to bring in uniformity in the practices followed by the manufacturers within the countries or in different regions. The guidelines provide the requirements in sufficient details in a simple and straightforward manner, to help in their easy understanding and implementation. The immediate requirement of our country is of developing a stability guideline on existing/generic drugs and products.

A preview of the guidelines available at the country and International levels on existing drugs will be relevant here. The ICH harmonized tripartite guideline Stability Testing of New Drug Substances and Products was published in 1993 and since then it has become an industry standard for stability evaluation of new molecular entities (new drug substances) and associated products. The Foreword of this guideline states that "the stability requirements specific to generic drugs ... were not considered in the development of this guideline". The World Health Organization (WHO) in the meantime, being an observer to the ICH, felt that the ICH parent stability guideline (Q1A) was unfit for universal application. The reasons were: i) the guideline Q1A did not address the extreme climatic conditions found in many countries, and ii) it only covered new drug substances and products and not the already established products that were in circulation in the WHO umbrella countries. WHO accordingly came out with a separate 'Guideline for Stability Testing of Pharmaceutical Products Containing Well Established Drug Substances in Conventional Dosage Forms'. It appeared in 1996 as Annex 5 to the thirty-fourth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (WHO Technical Report Series 863, WHO, Geneva). Later, the Committee for Proprietary Medicinal Products (CPMP) under the European Agency for the Evaluation of Medicinal Products (EMEA) also adopted a guideline coded CPMP/QWP/556/96 entitled 'Note for Guidance on Stability Testing of Existing Active Substances and Related Finished Products' for those seeking marketing authorization for medicinal products in European Union. This guideline is under revision and a draft guideline under the title 'Note for Guidance on Stability Testing: stability Testing of Existing Active Substances and Related Finished Products' was released for consultation lately in February 2002. On its part, the Therapeutic Products Directorate, Canada also issued a guideline on stability testing of existing drug substances and products in 1997. US FDA issued a draft version of the guidance for industry under the title - Stability Testing of Drug Substances and Drug Products in June 1998. The guidance discusses stability testing for New Drug Applications (NDA), Abbreviated New Drug Applications (ANDA) and the Investigational New Drug Applications (IND). There also exists a plan of ICH to develop a separate guideline for generic drugs, coded as Q1G, but due to lack of consensus among the ICH states, some difficulty is being encountered in framing of this guidance. However, a recent development of interest is the issue of draft guideline Q1F by ICH under the title 'Stability Data Package for Registration in Climatic Zones III and IV. This guideline recommends long-term storage condition of 30 °C/65% RH for climatic zones III and IV, which also becomes an intermediate test condition for climatic zones I and II. This new storage condition replaces 30 °C/60% RH, which was earlier suggested in ICH parent guideline Q1AR as intermediate test storage condition and for real time testing of products in zones III and IV in the WHO guideline. The WHO has endorsed this change and notification has already appeared in EC37 draft report.

This guideline serves to describe stability requirements for existing drug substances and products in circulation in India and it seeks to encompass typical country requirements.

1.3 SCOPE

This guideline addresses the stability testing information to be included in submissions on existing drug substances and related drug products. For the purpose of this guideline, an existing drug substance and associated drug product are those that have been authorised previously in the country. This guideline is not intended for application to new drugs. For them, ICH guidelines can be followed, with suitable modifications in stress test and storage conditions, similar to those advised in this guideline.

This guideline applies to drugs, including synthetic, semi-synthetic, and drugs produced from fermentation or derived from natural sources. It does not apply to radiopharmaceuticals, biologicals and products derived by biotechnology.

2. DRUG SUBSTANCE

2. DRUG SUBSTANCE

2.1 GENERAL

Information on the stability of the drug substance is an integral part of the systematic approach to stability evaluation.

2.2 STRESS TESTING

Stress testing helps to determine the intrinsic stability of the molecule by establishing degradation pathways in order to identify the likely degradation products and to validate the stability-indicating power of the analytical procedures used. It is conducted in more exaggerated conditions than accelerated test conditions (defined later in this guideline). For practical conduct of stress testing, guidance is provided in literature3 which may be followed. Stress testing is generally conducted on a single batch of the drug substance. The testing covers influence of temperature, pH, humidity, oxidation and light.

Generally, no stress tests may be required if drug substance is covered by pharmacopoeial monograph and the degradation products are named under "purity test' and/or 'impurities'. Otherwise, when available, relevant data available in the public domain can also be provided to support the proposed degradation pathways. For established drugs, information on decomposition process and intrinsic stability is usually available in scientific literature, like published papers and the monographs contained in book series titled 'Analytical Profiles of Drugs Substances4. Useful information is also contained in the treatise by Connors5 and those on stability-indicating assays6,7.

Practically, stress testing is required if no data are available in the literature or the official pharmacopoeias. Still, it may not be necessary to examine specifically for certain degradation products if it is indicated that they are not formed under accelerated or long-term storage conditions.

2.3 FORMAL STUDIES

Primary stability studies are intended to show that the drug substance will remain within specification during the re-test or shelf period if stored under recommended storage conditions in the proposed bulk storage container. The re-test period is determined for stable drugs, while the shelf-life period is determined for degradable drugs. Drugs listed in the WHO list of degradable drugs (see Annexure) may be considered for labelling with the shelf-life period.

The re-test and shelf life period is based on the results of long-term stability studies performed using validated analytical procedures. In certain cases, information available in the public domain may be sufficient to establish an appropriate re-test date, e.g. when a substantial body of evidence exists that establishes that the drug is inherently stable. In all instances, total relevant information available on the stability of the drug substance should be provided.

The submission should include either

a. a re-test period for the drug substance, after which any batch must be re-tested for compliance with specification and then used within a month,

or

b. a commitment that the drug substance will be tested for compliance with the pharmacopoeial monograph immediately prior to use in the manufacture of the drug product. In this case, formal stability studies will not be required (This clause applies to drug substances described in the official pharmacopoeial monograph, which covers the degradation products and for which suitable limits have been set but a re-test period is not defined),

or

c. an expiration period for the drug substance (necessary only for degradable drugs).

Notes:

i) The assignment of a re-test period de-links the stability of drug substance from that of the drug product. In both cases, independent and real stability data are necessary to justify the labelled claims. In case a manufacturer wishes to assign an expiry period to the drug product, beyond the expiry date of a degradable drug substance, this should be supported by both accelerated and real time studies.

ii) For guidance on classification of drugs into degradable and stable categories, it is suggested that WHO lists given in Annexure be consulted.

2.4 SELECTION OF BATCHES

Formal studies should consist of accelerated and long-term testing on at least two different pilot/production batches for stable drug substances. In contrast, samples should be taken from three primary batches of easily degradable drug substances on which limited stability data are available.

When production is being carried out at different sites or by different methods, stability studies may not be required on material from each source provided equivalence is confirmed through certificate of analysis of three validation batches and certificate of successful validation that material from all sources or production methods meets the specifications, including purity, moisture and when relevant, crystal form. In such instances, the potential impact on re-test periods of differences in the storage/distribution packaging to be used by different drug substance manufacturers must be assessed.

Note: When more than one site or production method for drug substance is described in the submission, at least two production batches of drug product manufactured using drug substance from each site or route/method should be placed on long-term stability studies using the same protocol as in the approved submission.

2.5 TEST PROCEDURES AND STABILITY-INDICATING ASSAY METHODS

The testing should cover those features susceptible to change during storage and likely to influence quality, safety and/or efficacy. Stability information should cover as necessary the physical, chemical and microbiological test characteristics. Validated stability-indicating assay methods8 must be applied. The analytical method may not be specific to each degradation product, but must be validated for specificity to the drug in their presence. In this regard, titrimetric, spectrophotometric. GC or HPLC assays prescribed in the current Pharmacopoeias may be used, subject to confirmation that they are specific when applied to degraded drug samples.

2.6 SPECIFICATIONS - SHELF LIFE

Specifications for pharmacopoeial drugs should be those specified in the monograph. For non-pharmacopoeial drugs, these should include individual and total upper limits for impurities, including degradation products, the justification for which should be based on safety considerations.

2.7 STORAGE TEST CONDITIONS

The length of the studies and the storage conditions should be sufficient to cover storage, shipment and subsequent use. Application of the same storage conditions as applied to the drug product will facilitate comparative review and assessment.

Recommended storage conditions and duration of studies at the time of filing in general cases are normally as follows:

Study Type	Storage Conditions	Minimum time period at submission
Long-term Testing	30°C ± 2°C/65% RH ± 5% RH	12 months
Accelerated Testing	40°C ± 2°C/75% RH ± 5% RH	6 months

Other storage conditions are allowable, if justified. In particular, temperature sensitive drug substances should be stored under an alternative, lower temperature condition, which will then become the designated long-term testing storage temperature. The accelerated testing should then be carried out at a temperature at least 15°C above this designated long-term storage temperature (together with the appropriate relative humidity conditions for that temperature).

To evaluate the impact of short-term excursions outside the label storage conditions, such as might occur during shipping, additional study data should be made available, for example, up to 3 months at 45-50°C (for distribution in hot and dry areas), or with 75%RH (distribution in humid areas or in rainy season).

Where "significant change" occurs during storage under accelerated testing conditions at 40°C ± 2°C/75% RH ± 5%, or if these conditions are inappropriate for physical reasons, the testing should be conducted only under long-term conditions.

A significant change is considered to have occurred if:

- the assay value shows a 5% decrease as compared with the initial value of a batch
- any specified degradation product is present in amounts greater than its specification limit
- the specification of appearance and physical properties are no longer met.

In all cases, the designated long-term testing conditions should be reflected in the labelling and re-test date.

The long-term testing should be continued for a sufficient period of time beyond one year to cover all appropriate re-test and shelf-life periods. Further accumulated long-term and accelerated data can be submitted to the competent authority for the grant of extension.

Drug substances intended for storage in a refrigerator

The following are the recommended storage conditions:

Study	Storage condition	Minimum time period covered by data at submission
Long term	5°C ± 3°C	12 months
Accelerated If available	25°C ± 2°C/60% RH ± 5% RH, otherwise 30°C ± 2°C/65% RH ± 5% RH	6 months

If significant change occurs between 3 and 6 months' testing at the accelerated storage condition, the proposed shelf life should be based on the real time data available from the long-term storage condition.

If significant change occurs within the first 3 months' testing at the accelerated storage condition, a discussion should be provided to address the effect of short term excursions outside the label storage condition, e.g., during shipment and handling. This discussion can be supported, if appropriate, by further testing on a single batch of the drug product for a period shorter than 3 months but with more frequent testing than usual. It is considered unnecessary to continue to test a drug substance through 6 months when a significant change has occurred within the first 3 months.

Drug substances intended for storage in a freezer

Study	Storage condition	Minimum time period covered by data at submission
Long term	- 20°C ± 5°C	12 months

For drug substances intended for storage in a freezer, the shelf life should be based on the real time data obtained at the long-term storage condition. In the absence of an accelerated storage condition for drug substances intended to be stored in a freezer, testing on a single batch at an elevated temperature (e.g., 5°C ± 3°C or 25°C ± 2°C) for an appropriate time period should be conducted to address the effect of short term excursions outside the proposed label storage condition.

Drug substances intended for storage below -20°C

Drug substances intended for storage below -20°C should be treated on a case-by-case basis.

2.8 TESTING FREQUENCY

The frequency of testing at the long term storage condition should normally be every 3 months over the first year, every 6 months over the second year, and annually thereafter through the proposed shelf life.

At the accelerated storage condition, a minimum of three time points, including the initial and final time points (e.g., 0, 3, and 6 months), from a 6-month study is recommended. Where an expectation (based on development experience) exists that results from accelerated testing are likely to approach significant change criteria, increased testing should be conducted by increasing the number of time points in the first three-month period.

2.9 PACKAGING/CONTAINERS

The testing should be done in containers that are either same or simulate the actual packaging used for storage and distribution of the drug substance. For example, a 1 Kg fibre drum lined with a polyethylene film and an external metal ring put in a similar manner as on a bigger

drum is a suitable prototype.

2.10 EVALUATION

The design of the stability study is to establish, based on testing of a minimum of at least two batches of the drug substance and evaluating the stability information (covering, as necessary, the physical, chemical (assay) and microbiological test characteristics), to determine a re-test period or shelf-life applicable to all future batches of the bulk drug substance manufactured and packaged under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification until the re-test date.

A re-test period for a drug substance may be established based on the available data from accelerated and long-term stability studies using the 95% confidence limit method (see 'Evaluation' under 'Drug products' for details). If the data shows so little degradation and so little variability that it is apparent from looking at the data that specifications would be easily met, a re-test period of 24 months may be granted without resorting to formal statistical analysis, providing a justification of omission should be sufficient.

A re-test date should be placed on the storage container and on the shipping container for a bulk drug substance. A drug substance batch may be used without re-test during an approved re-test period. However, beyond the approved re-test period, any remaining portion of the batch should be re-tested immediately before use. Re-test of different portions of the same batch for use at different times as needed is acceptable, provided that the batch has been stored under the defined conditions, the test methods are validated and stability-indicating, and all stability-related attributes are tested and test results are satisfactory.

Satisfactory re-test results on a drug substance batch after the re-test date do not mean that the re-test period can be extended for that batch or any other batch. The purpose of re-test is to qualify a specific batch of a drug substance for use in the manufacture of a drug product, rather than to re-certify the drug substance with a new re-test date. To extend the re-test period, full long-term data from a formal stability study on two pilot/production batches using a protocol approved in an application should be provided. A re-test period for a drug substance may be extended beyond what was approved in the original application. This can be achieved based on full long-term stability data (i.e., covering the desired re-test period on three production batches using an approved stability protocol).

In a case where testing reveals a limited shelf life for a drug substance, it may be inappropriate to use a re-test date. An expiration period, rather than a re-test period, should be established for a drug substance with a limited shelf life (e.g., some antibiotics).

The evaluation may consider assay and other appropriate attributes for stable products, but for others, the levels of degradation products should also be considered.

2.11 LABELLING

The stated storage conditions (temperature, light, humidity) should be based on the stability evaluation of the drug substance. As a minimum, a storage temperature range or maximum should be specified (in degrees Celsius). Where applicable, specific requirements should be stated, e.g. "Protect from light", "Protect from freezing". Note: The use of precautionary statements should not be a substitute for selecting the appropriate packaging system for the bulk drug substance.

The use of terms such as "ambient conditions" or "room temperature" is unacceptable.

3. DRUG PRODUCTS

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3.1 GENERAL

The design of the stability programme for the finished product should be based on the knowledge of the behaviour and properties of the drug substance and the dosage form.

3.2 STRESS TESTING

Selected stress testing directly on a drug product may be accepted for the purpose of establishment of validated stability-indicating assay method, if it is proved that no physical change occurs in the drug product over the stress period. The following conditions are suggested for stress testing of drug products:

a. Increments of 5°C or 10°C higher than accelerated temperature of 40°C to cover study of the influence of dry heat. This test is to simulate hot conditions faced by products during transportation and shipment.

b. Additional exposure to 2-8 °C (refrigerator) may be necessary for injections, suspensions and oral liquids to check crystallization of sugar or other ingredients. Similarly, specific tests like study at subzero temperatures and freeze-thaw and thermal cycling may be conducted, as required dependent upon the dosage form.

c. Simultaneous exposure to 40°C, 75% RH and a minimum of 1.2 million lux h fluorescent light and 200W h/m2 UVA light. This test is meant to study the influence of tropical conditions on the drug products.

The stress testing should be done on a single batch of the product, which must be of the same composition and quality as the marketing batch, including the packaging. The stress tests are normally conducted for a total period of 3 months. The samples are observed for physical changes at regular intervals and drawn for analysis either fortnightly or monthly or a period suitable. The study can be discontinued in-between, if it serves the purpose of establishment of the specificity of an analytical method. For those tests that are specific to dosage forms, the period of testing however may vary on case-to-case basis.

Testing on unprotected drug product should form part of the stress studies, for package evaluation.

3.3 SELECTION OF BATCHES

Stability information from accelerated and long-term testing should be provided on batches of the same formulation and dosage form in the containers and closure proposed for marketing. Normally, it is necessary to study several batches of the drug product to obtain reliable stability information. However, as few as two primary batches may be sufficient under certain conditions, e.g., a conventional dosage form containing a drug substance known to be fairly stable. For degradable substances, a minimum of three primary batches should be tested. The manufacturing process used for pilot scale batches, included in the study, should meaningfully simulate that which would be applied to large-scale batches for marketing. The process should provide product of the same quality intended for marketing, and meeting the same quality specifications as to be applied for release material.

Where possible, batches of the finished product should be manufactured using identifiably different batches of drug substance.

Data on laboratory scale batches is not acceptable as primary stability information. Data on associated formulations or packaging may be submitted as supportive information.

It is expected that at least the first two production scale batches manufactured or sold post-approval should be placed on long-term stability studies using the post-market stability protocols described in the approved submission.

3.4 TEST PROCEDURES AND TEST CRITERIA

The testing should cover those features susceptible to change during storage and likely to influence quality, safety and/or efficacy. Analytical test procedures should be fully validated and the assays should be stability indicating. The stability testing should cover chemical as well as physical and microbiological attributes, as described below:

Attribute	Requirements
Chemical	Drug products remain within registered limits for drug content and related substances/impurities.
Physical	Physical properties, including appearance, palatability, uniformity, dissolution, and suspendability are acceptable and specific properties like particle size/surface areas remain within limits.
Microbiological	Sterility or resistance to microbiological growth is retained according to specific requirements. Preservative that are present retain effectiveness within the specified limits.

The following list of parameters for each dosage form is presented as a guide for the types of tests to be included in a study. The list is not intended to be exhaustive, nor it is expected that every test be included in the design of a stability protocol for a particular drug product. Furthermore, it is not expected that every listed test be performed at each time point.

Dosage Form	Test parameters
Tablets	Appearance, color, odor, assay, disintegration/dissolution, moisture and friability or hardness testing.
Hard gelatin capsules	Appearance, color, odor of contents, assay, disintegration/dissolution, moisture and microbial limits. Soft gelatin capsules Appearance, color, odor of contents, assay, disintegration/dissolution, moisture, microbial limits, pH, leakage and pellicle formation.
Emulsions	Appearance including phase separations, color, odor, assay, pH, viscosity, preservative content, weight loss and microbial limits.
Oral solutions and suspensions (Samples of suspensions should be prepared for assay according to recommended labelling (e.g., shake well before using).	Appearance including formation of precipitate, color, odor, assay, pH, preservative content, weight loss and microbial limits. For suspensions additional parameters are: redispersibility, viscosity, and mean size and distribution of particles.
Oral powders for reconstitution: Oral Powder Reconstituted Product (solutions and suspensions)	Appearance, color, odor, moisture and reconstitution time. Appearance including formation of precipitate, color, odor, assay, pH, preservative content, weight loss and microbial limits. For suspensions additional parameters are: redispersibility, rheological parameters and mean size and distribution of particles.
Topical, Opthalmics and Otic preparations (Ointments, creams, pastes, gels, lotions, solutions)	Appearance, clarity, color, odor, assay, pH, resuspendibility (for lotions), consistency, viscosity, particle size distribution (for suspensions, when feasible) preservative and antioxidant content (if present), microbial limits/ sterility and weight loss (when appropriate). Ophthalmic or otic products should be additionally evaluated for sterility, particulate matter and extractables.
Suppositories	Appearance, color, assay, particle size, softening range, apperance, dissolution (at 37°C), and microbial limits.
Small volume parenterals: Drug injection	Appearance, color, assay, pH, preservative content, particulate matter, sterility and pyrogenicity/bacterial endotoxin.
Small volume parenterals: Drug for injection: Powder	Appearance, color, moisture content and reconstitution time.
Small volume parenterals: Drug for injection: Reconstituted product	Appearance, color, assay, pH, preservative content, particulate matter, sterility and pyrogenicity/bacterial endotoxin.
Large volume parenterals	Appearance, color, assay, pH, preservative content, particulate matter, sterility and pyrogenicity/bacterial endotoxin.
Metered dose inhalations and nasal aerosols	Appearance (including content, container,valve and its components), color, taste, assay, assay for co-solvent (if applicable), dose content uniformity, labeled number of medication actuations per container meeting dose content uniformity, aerodynamic particle size distribution, microscopic evaluation, water content, leak rate, microbial limits, valve delivery (shot weight), extractables/leachables from plastic and elastomeric components. Because the inhalant drug products are intended for use in the respiratory system, confirmation that initial release specifications are maintained should be provided to ensure the absence of pathogenic organisms (e.g., Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli, and Salmonella species) and that the total aerobic count and total mold and yeast count per canister are not exceeded.
Suspensions type of aerosols	Microscopic evaluation of appearance of the valve components and container's contents for large particles, changes in morphology of the drug surface particles, extent of agglomerates, crystal growth, foreign particulate matter, corrosion of the inside of the container or deterioration of the gaskets
Inhalation solutions and powders	Appearance, color, assay, pH, sterility, particulate matter, preservative and antioxidant content (if present), net contents (fill weight /volume), weight loss, extractables/leachables from plastic, elastomeric and other packaging components. **Additional tests for inhalation powders** Aerodynamic particle size distribution of the emitted dose, microscopic evaluation, microbial limit, moisture content, foreign particulates, content uniformity of the emitted dose, and number of medication doses per device meeting content uniformity of the emitted dose (device metered products).
Nasal sprays: Solutions and suspensions equipped with a metering Pump	Appearance, color, clarity, assay, degradation products, preservative and antioxidant content, microbial limits, pH, particulate matter, unit spray medication content uniformity, number of actuations meeting unit spray content uniformity per container, droplet and/or particle size distribution, weight loss, pump delivery,

	microscopic evaluation (for suspensions), foreign particulate matter, extractables/ leachables from plastic and elastomeric components of the container, closure, and pump.
Transdermals (Devices applied directly to the skin for the purpose of continuously infusing a drug substance into the dermis through the epidermis)	Appearance, assay, leakage, microbial limit/sterility, peel and adhesive forces, drug release rate.
Implantable, subdermal, vaginal and intrauterine devices that deliver drug products	Total drug substance content, extractables, in vitro drug release rate, microbial burden or sterility (as appropriate) Stability testing for intrauterine devices (IUDs) Deflection of horizontal arms or other parts of the frame if it is not a T-shaped device (frame memory), tensile strength of the withdrawal string, integrity of the package (i.e., seal strength of the pouch), sterility of the device.

Wherever applicable, samples should be stored in upright and inverted (or on-the-side) orientations to allow for interaction between closure and the container.

3.5 SPECIFICATIONS -SHELF LIFE

Limits of acceptance for pharmacopoeial products should be those specified in the compendia. For non-pharmacopoeial products, these should be derived from acceptable and justifiable deviations from release specifications based on the stability evaluation and changes observed on storage. It will be required to include specific upper limits for degradation products, the justification for which should be based on safety and/or efficacy considerations as well as on levels of degradation products observed in batches placed on stability studies. More stringent release specifications may be required in certain cases in order to ensure that shelf-life specifications are met throughout the labelled expiration period of the drug product.

Where necessary, the justification for the limits proposed for certain other tests such as particle size and/or dissolution rate will require reference to the results observed for batch(es) used in bioequivalence, comparative bioavailability or clinical studies. Any differences between the release and shelf life specifications for anti-microbial preservatives should be supported by preservative efficacy testing at the lower shelf-life limits.

3.6 STORAGE TEST CONDITIONS

The length of the studies and the storage conditions should be sufficient to cover storage, shipment and subsequent use (e.g., reconstitution or dilution as recommended in the labelling). In all cases, the designated long-term testing conditions should be reflected in the labelling. The long-term testing should be continued for a sufficient period of time beyond one year to cover all appropriate shelf-life periods. Further accumulated long-term and accelerated data can be submitted to the competent authority for the grant of extension.

The following storage conditions are suggested for different types of products:

General products	Study Storage Condition	Minimum Time Periodat Submission
Long-term Testing	30°C ± 2°C/65% RH ± 5%	12 months
Accelerated Testing	40°C ± 2°C/75% RH ± 5%	6 months

Where "significant change" occurs due to accelerated testing, only long-term testing should be conducted.
"Significant change" at 40°C/75% RH is defined as:

1. A 5% potency loss from the initial assay value of a batch;

2. Any specified degradation product exceeding its acceptance criterion;

3. Failure to meet specifications for appearance, physical properties and functionality test (e.g., color, phase separation, resuspendability, dose delivery per actuation, caking, hardness, etc.). Some changes in physical attributes (e.g., softening of suppositories, melting of creams) may be expected under accelerated conditions;
4. Failure to meet specification limits for pH; and/or

5. Failure to meet specification limit for dissolution of capsules or tablets.

Other storage conditions are allowable if justified. The storage conditions for some distinct product categories are described below:

Drug products packaged in impermeable containers

Sensitivity to moisture or potential for solvent loss is not a concern for drug products packaged in impermeable containers that provide a permanent barrier to passage of moisture or solvent. Thus, stability studies for products stored in impermeable containers can be conducted under any controlled or ambient humidity condition. It means that the samples can be put even in same humidity chambers that are under use in 'General products'.

Liquid products packaged in semi-permeable containers

Aqueous-based products packaged in semi-permeable containers should be evaluated for potential water loss in addition to physical, chemical, and microbiological stability. This evaluation can be carried out under conditions of low relative humidity, as discussed below. Ultimately, it should be demonstrated that aqueous-based drug products stored in semi-permeable containers can withstand low relative humidity environments.

Other comparable approaches can be developed and reported for non-aqueous, solvent-based products.

Study	Storage condition	Minimum time period covered by data at submission
Long term	30°C ± 2°C/40% RH ± 5% RH	12 months
Accelerated	40°C ± 2°C/not more than (NMT) 25% RH	6 months

Where "significant change" occurs due to accelerated testing, only long-term testing should be conducted. A significant change in water loss alone at the accelerated storage condition does not necessitate testing at long-term storage condition. However, data should be provided to demonstrate that the drug product will not have significant water loss throughout the proposed shelf life if stored at 30°C and the reference relative humidity of 40% RH.

A 5% loss in water from its initial value is considered a significant change for a product packaged in a semi-permeable container after an equivalent of 3 months' storage at 40°C/NMT 25% RH. However, for small containers (1 mL or less) or unit-dose products, a water loss of 5% or more after an equivalent of 3 months' storage at 40°C/NMT 25% RH may be appropriate, if justified.

An alternative approach to studying at the reference relative humidity as recommended in the table above (for either long term or accelerated testing) is performing the stability studies under higher relative humidity and deriving the water loss at the reference relative humidity through calculation. This can be achieved by determining the permeation coefficient for the container/closure system experimentally or, as shown in the example below, using the calculated ratio of water loss rates between the two humidity conditions at the same temperature. The permeation coefficient for a container closure system can be experimentally determined by using the worst-case scenario (e.g., the most diluted of a series of concentrations) for the proposed drug product.

For a product in a given container closure system, container size, and fill, an appropriate approach for deriving the water loss rate at the reference relative humidity (RRH) is to multiply the water loss rate measured at an alternative relative humidity (ARH) at the same temperature by a water loss rate ratio shown in the table below:

ARH	RRH	Water loss ratio at 40°C
60% RH	25% RH	1.9
60% RH	40% RH	1.5
75% RH	25% RH	3.0

A linear water loss rate at the alternative relative humidity over the storage period should be demonstrated.

Drug products intended for storage in a refrigerator

The following are the recommended storage conditions:

Study	Storage condition	Minimum time period covered by data at submission
Long term	5°C ± 3°C	12 months
Accelerated If available,	25°C ± 2°C/60% RH ± 5% RH, otherwise30°C ± 2°C/65% RH ± 5% RH	6 months

If the drug product is packaged in a semi-permeable container, appropriate information should be provided to assess the extent of water loss.

If significant change occurs between 3 and 6 months' testing at the accelerated storage condition, the proposed shelf life should be based on the real time data available from the long-term storage condition.

If significant change occurs within the first 3 months' testing at the accelerated storage condition, a discussion should be provided to address the effect of short term excursions outside the label storage condition, e.g., during shipment and handling. This discussion can be supported, if appropriate, by further testing on a single batch of the drug product for a period shorter than 3 months but with more frequent testing than usual. It is considered unnecessary to continue to test a product through 6 months when a significant change has occurred within the first 3 months.

Drug products intended for storage in a freezer

Study	Storage condition	Minimum time period covered by data at submission
Long term	- 20°C ± 5°C	12 months

For drug products intended for storage in a freezer, the shelf life should be based on the real time data obtained at the long-term storage condition. In the absence of an accelerated storage condition for drug products intended to be stored in a freezer, testing on a single batch at an elevated temperature (e.g., 5°C ± 3°C or 25°C ± 2°C) for an appropriate time period should be conducted to address the effect of short term excursions outside the proposed label storage condition.

Drug products intended for storage below -20°C

Drug products intended for storage below -20°C should be treated on a case-by-case basis.

3.7 TESTING FREQUENCY

The frequency of testing at the long term storage condition should normally be every 3 months over the first year, every 6 months over the second year, and annually thereafter through the proposed shelf life.

At the accelerated storage condition, a minimum of three time points, including the initial and final time points (e.g., 0, 3, and 6 months), from a 6-month study is recommended. Where an expectation (based on development experience) exists that results from accelerated testing are likely to approach significant change criteria, increased testing should be conducted by increasing the number of time points in the first three-month period.

Reduced designs9, i.e., matrixing or bracketing, where the testing frequency is reduced or certain factor combinations are not tested at all, can be applied, if justified.

3.8 PACKAGING/CONTAINERS

The testing should be carried out in the final packaging proposed for marketing. Additional testing of unprotected finished product can form a useful part of the stress testing and pack evaluation, as can studies carried out in other related packaging materials in supporting the definitive pack(s).

3.9 STABILITY COMMITMENT

When available long-term stability data on primary batches do not cover the proposed shelf life granted at the time of approval, a commitment should be made to continue the stability studies post approval in order to firmly establish the shelf life. Where the submission includes long-term stability data from required number of batches covering the proposed shelf life, a post approval commitment is considered unnecessary.

Otherwise, one of the following commitments should be made:

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

2. If the submission includes data from stability studies on fewer than required batches, a commitment should be made to continue the long-term studies through the proposed shelf life and the accelerated studies for 6 months, and to place additional batches on long-term stability studies through the proposed shelf life and on accelerated studies for 6 months.

3. If the submission does not include stability data on production batches, a commitment should be made to place the first two or three production batches on long-term stability studies through the proposed shelf life and on accelerated studies for 6 months.

The stability protocol used for studies on commitment batches should be the same as that for the primary batches, unless otherwise scientifically justified.

3.10 EVALUATION

The purpose of the stability study is to establish, based on testing a minimum of two (stable drug substance) or three (degradable drug substance) batches of the drug product, a shelf life and label storage instructions applicable to all future batches of the drug product manufactured and packaged under similar circumstances. Therefore, a systematic approach should be adopted in the presentation and evaluation of the stability information, which should include, as appropriate, results from the physical, chemical, and microbiological tests, including particular attributes of the dosage form (as listed in Section 3.4).

A maximum shelf life of 24 months is to be assigned to a drug product in the first instance. If real time data is supported by results from accelerated studies, the shelf life may be extended beyond the end of real time studies. Normally extrapolation to twice the length of the real time studies can be accepted. For example, if results are satisfactory, 12 months long-term and 6 months accelerated storage data would normally be considered sufficient to grant an expiration period of 24 months. The shelf life of 24 months is directly assigned, provided also that i) the drug substance is known to be stable, ii) supporting data indicate that similar formulations have been assigned a shelf-life of 24 months or more, and iii) the manufacturer continues to perform the real time studies until the proposed shelf-life is covered. Where application of this rule-of-thumb is not warranted due to the lack of sufficient accelerated testing data, an expiration period of 24 months may nonetheless be acceptable provided satisfactory results are available from at least 3 months accelerated testing and 18 months long-term testing.

Otherwise, an acceptable statistical approach to determine shelf life involves evaluation of the time at which the 95% one-sided confidence limit for the mean degradation curve intersects the acceptable lower specification limit. Here due consideration should be given to batch-to- batch analysis (three batches), and if it shows that variability is small, the data are advantageously combined into one overall estimate. The similarity of the estimated curves among the batches tested should be assessed by applying statistical tests of the equality of slopes and of zero time intercepts. The level of significance of the tests, expressed in the p-value, should be chosen so that the decision to combine the data is made only if there is strong evidence in favour of combining. A p-value of 0.25 for preliminary statistical tests has been recommended. If the tests for equality of slopes and for equality of intercepts do not result in rejection at a level of significance of 0.25, the data from the batches could be pooled. If these tests resulted in p-values less than 0.25, a judgment should be made as to whether pooling could be permitted. If the preliminary statistical test rejects the hypothesis of batch similarity because of unequal initial intercept values, it may still be possible to establish that the lines are parallel (i.e., that the slopes are equal). If so, the data may be combined for the purpose of estimating the common slope. The individual expiration period for each batch in the stability study may then be determined by considering the initial values and the common slope using appropriate statistical methodology. If data from several batches are combined, as many batches as feasible should be combined because confidence limits about the estimated curve will become narrower as the number of batches increases, usually resulting in a longer expiration period. If it is inappropriate to combine data from several batches, the overall expiration period will depend on the minimum time a batch may be expected to remain within acceptable limits.

The nature of the degradation relationship will determine the need for transformation of the data for linear regression analysis. Usually the relationship can be represented by a linear, quadratic or cubic function on an arithmetic or logarithmic scale. Statistical methods should be employed to test the goodness of fit on all batches and combined batches (where appropriate) to the assumed degradation line or curve.

The extension of shelf life beyond 24 months is granted only after satisfactory long-term data is generated in an on-going stability testing. The extension to 36 months is made after 36 months long-term study is completed and annual reports are submitted. Further extensions would require submission of similar annual reports of on-going long-term testing.

The computation of the expiration period of the drug product should begin no later than the time of quality control release of that batch, and the date of release should generally not exceed 30 days from the production date, regardless of the packaging date. If the expiration date includes only a month and year, the product should meet specifications through the last day of the month. If the production batch contains reprocessed material, the expiration period should be computed from the date of manufacture of the oldest reprocessed material used.

The stability of the drug product after reconstituting or diluting according to labelling should be addressed to provide appropriate and supportive information.

When warranted, a previously approved expiration period may be shortened. The supplemental application be submitted and should provide pertinent information and the data that led to the shortening of the expiration period. The expiration period should be shortened to the nearest available real-time long-term test point where the product meets acceptance criteria. The expiration period thus derived should be applied to all subsequent production batches and may not be extended until the cause for the shortening is fully investigated, the problem is resolved, and satisfactory stability data become available on at least three new production batches to cover the desired expiration period and are submitted in a changes-being-effected supplement.

Intermediates such as blends, triturates, cores, extended-release beads or pellets may be held for up to 30 days from their date of production without being re-tested prior to use. An intermediate that is held for longer than 30 days should be monitored for stability under controlled, long-term storage conditions for the length of the holding period. In addition, the first production batch of the finished drug product manufactured with such an intermediate should be monitored on long-term stability. When previous testing of an intermediate or the related drug product batches suggests that an intermediate may not be stable for 30 days, the holding time should be kept to a minimum and qualified by appropriate stability testing. This clause also extends to bulk formulations awaiting packaging.

3.11 LABELLING

The stated storage conditions (temperature, light, humidity) should be based on the stability evaluation of the drug product. As a minimum, a storage temperature range or maximum must be specified (in degrees Celsius). The use of terms such as "ambient conditions" or "room temperature" is unacceptable.

Where applicable, specific requirements should be stated, e.g. "Protect from light", "Protect from freezing". Note: The use of precautionary statements should not be a substitute for selecting the appropriate packaging system for the drug product.

When only a maximum storage temperature is proposed (e.g. "Store up to 30°C"), it may be required to demonstrate that the product is not adversely affected by freezing or storage under refrigerated conditions (2°C to 8°C).

4. GLOSSARY

4. GLOSSARY

The following definitions are provided to facilitate interpretation of the guideline.

Accelerated testing

Studies designed to increase the rate of chemical degradation or physical change of a drug substance or drug product by using exaggerated storage conditions as part of the formal stability studies. Data from these studies, in addition to long term stability studies, can be used to assess longer term chemical effects at non-accelerated conditions and to evaluate the effect 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 changes.

Bracketing

The design of a stability schedule such that only samples on the extremes of certain design factors, e.g., strength, package size, are tested at all time points as in a full design. The design assumes that the stability of any intermediate levels is represented by the stability of the extremes tested. Where a range of strengths is to be tested, bracketing is applicable if the strengths are identical or very closely related in composition (e.g., 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).

Bracketing can be applied to different container sizes or different fills in the same container closure system.

Commitment batches

Production batches of a drug substance or drug product for which the stability studies are initiated or completed post approval through a commitment made in the registration application.

Container closure system

The sum of packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection to the drug product. A packaging system is equivalent to a container closure system.

Dosage form

A pharmaceutical product type (e.g., tablet, capsule, solution, cream) that contains a drug substance generally, but not necessarily, in association with excipients.

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

Drug substance

The unformulated drug substance that may subsequently be formulated with excipients to produce the dosage form.

Excipient

Anything other than the drug substance in the dosage form.

Expiration date
The date placed on the container label of a drug product designating the time prior to 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.

Formal stability studies

Long term and accelerated (and intermediate) studies undertaken on primary and/or commitment batches according to a prescribed stability protocol to establish or confirm the re-test period of a drug substance or the shelf life of a drug product.

Impermeable containers

Containers that provide a permanent barrier to the passage of gases or solvents, e.g., sealed aluminum tubes for semi-solids, sealed glass ampoules for solutions.

Long term testing

Stability studies under the recommended storage condition for the re-test period or shelf life proposed (or approved) for labeling.

Matrixing

The design of a stability schedule such that a selected subset of the total number of possible samples for all factor combinations is tested at a specified time point. At a subsequent time point, another subset of samples for all factor combinations is tested. The design assumes that the stability of each subset of samples tested represents the stability of all samples at a given time point. 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 closure system, and, possibly in some cases, different container closure systems.

Pilot scale batch

A batch of a drug substance or drug product manufactured by a procedure fully representative of and simulating that to be applied to a full production scale batch. For solid oral dosage forms, a pilot scale is generally, at a minimum, one-twentieth that of a full production scale or 50,000 tablets or capsules, whichever is the larger.

Primary batch

A batch of a drug substance or drug product used in a formal stability study, from which stability data are submitted in a registration application for the purpose of establishing a re-test period or shelf life, respectively. A primary batch of a drug substance should be at least a pilot scale batch. For a drug product, two of the three batches should be at least pilot scale batch, and the third batch can be smaller if it is representative with regard to the critical manufacturing steps. However, a primary batch may be a production batch.

Production batch

A batch of a drug substance or drug product manufactured at production scale by using production equipment in a production facility as specified in the application.

Re-test date

The date after which samples of the drug substance should be examined to ensure that the material is still in compliance with the specification and thus suitable for use in the manufacture of a given drug product.

Re-test period

The period of time during which the drug substance is expected to remain within its specification and, therefore, can be used in the manufacture of a given drug product, provided that the drug substance has been stored under the defined conditions. After this period, a batch of drug substance destined for use in the manufacture of a drug product should be re-tested for compliance with the specification and then used immediately. A batch of drug substance can be re-tested multiple times and a different portion of the batch used after each re-test, as long as it continues to comply with the specification. For most biotechnological/ biological substances known to be labile, it is more appropriate to establish a shelf life than a re-test period. The same may be true for certain antibiotics.

Semi-permeable containers

Containers that allow the passage of solvent, usually water, while preventing solute loss. The mechanism for solvent transport occurs by absorption into one container surface, diffusion through the bulk of the container material, and desorption from the other surface. Transport is driven by a partial-pressure gradient. Examples of semi-permeable containers include plastic bags and semi-rigid, low-density polyethylene (LDPE) pouches for large volume parenterals (LVPs), and LDPE ampoules, bottles, and vials.

Shelf life (also referred to as expiration period)

The time period during which a drug product is expected to remain within the approved shelf life specification, provided that it is stored under the conditions defined on the container label.

Specification - Release

The combination of physical, chemical, biological, and microbiological tests and acceptance criteria that determine the suitability of a drug product at the time of its release.

Specification - Shelf life

The combination of physical, chemical, biological, and microbiological tests and acceptance criteria that determine the suitability of a drug substance throughout its re-test period, or that a drug product should meet throughout its shelf life.

Storage condition tolerances

The acceptable variations in temperature and relative humidity of storage facilities for formal stability studies. The equipment should be capable of controlling the storage condition within the ranges defined in this guideline. The actual temperature and humidity (when controlled) 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, and reported if judged to affect stability results. Excursions that exceed the defined tolerances for more than 24 hours should be described in the study report and their effect assessed.

Stress testing

Such testing is part of the development strategy and is normally carried out under more severe conditions than those used for accelerated testing.

Supporting data

Data, other than those from formal stability studies, that support the analytical procedures, the proposed re-test period or shelf life, and the label storage statements. Such data include (1) stability data on early synthetic route batches of drug substance, small scale batches of materials, investigational formulations not proposed for marketing, related formulations, and product presented in containers and closures other than those proposed for marketing; (2) information regarding test results on containers; and (3) other scientific rationales.

5. REFERENCES

5. REFERENCES

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6. ANNEXURE

Annexure

LISTS OF DEGRADABLE AND STABLE SUBSTANCES
(REF: WHO/PHARM/86.529 WORLD HEALTH ORGANIZATION, GENEVA)

The essential drugs were subjected by WHO to stress degradation studies. All the substances were initially exposed for 30 days to air at 50°C and 100%RH. If no degradation was demonstrable at this time, the temperature was raised to 70 °C for a further period of 3-7 days. Light was excluded. Based on the results, the drugs were categorised as degradable and stable.

INDEX OF DEGRADABLE SUBSTANCES

Acetylsalicylic acid	Emetine hydrochloride
Aminophylline	Ephedrine
Amitriptyline hydrochloride	Ephedrine sulphate
Ammonium chloride	Epinephrine
Amphotericin B	Epinephrine hydrogen tartrate
Ampicillin sodium	Ergocalciferol
Ampicillin trihydrate	Ergometrine hydrogen maleate
Antimony sodium tartrate	Ergotamine maleate
Ascorbic acid	Ergotamine tartrate
	Ethosuximide
Bacitracin	Ethylmorphine hydrochloride
Bacitracin zinc	
Benzathine benzylpencillin	Ferrous sulphate
Benzylpencillin potassium	Fluphenazine decanoate
Benzylpencillin sodium	Fluphenazine hydrochloride
Bephenium hydroxynaphthoate	Formaldehyde solution
Calcium gluconate	Gentamicin sulphate
Calcium para-aminosalicylate	Guanethidine sulphate
Carbenicillin sodium	
Cefalexin	Hexylresorcinol
Chloral hydrate	Hydralazine hydrochloride
Chloramphenicol sodium succinate	Hydrocortisone sodium succinate
Chlorphenamine hydrogen maleate	Hydroxocobalamin
Chlorpromazine hydrochloride	Hyoscyamine sulphate
Chlortetracycline hydrochloride	
Cloxacillin sodium(monohydrate)	Imipramine hydrochloride
Coal tar	Ipecacuanha powder
Codeine phosphate	Isoprenaline hydrochloride
Colecalciferol	Isoprenaline sulphate
Cresol	
	Lidocaine hydrochloride
Dapsone	
Dexamethasone sodium phosphate	Melarsoprol
Dicloxacillin sodium (monohydrate)	Mercuric oxide yellow
Diethylcarbamazine dihydrogen citrate	Metrifonate
Doxycycline hyclate	
Naloxone hydrochloride	Quinine bisulphate
Neomycin sulphate	Quinine dihydrochloride
Nystatin	
	Retinol (Vitamin A)
Orciprenaline sulphate	
Oxytetracycline hydrochloride	Salbutamol sulfate
	Senna leaf
Paromycin sulphate	Silver nitrate
Penicillamine	Sodium calcium edetate
Pethidine hydrochloride	Sodium lactate
Phenobarbital sodium	Sodium nitrite
Phenoxymethylpencillin	Sodium para-aminosalicylate
Phenoxymethylpencillin calcium	Sodium stibogluconate
Phenoxymethylpencillin potassium	Sulfacetamide sodium
Phentolamine mesilate	Sulfadiazine sodium
Phenylbutazone	Suxamethonium chloride
Pilocarpine hydrochloride	
Pilocarpine nitrate	Tetracaine hydrochloride
Procainamide hydrochloride	Tetracycline hydrochloride
Procaine benzylpencillin	Thiamine hydrochloride
Procaine hydrochloride	Thiopental sodium
Procarbazine hydrochloride	Tolbutamide
Promazine hydrochloride	
Promethazine hydrochloride	Undecylenic acid
Pyridoxine hydrochloride	
	Warfarin sodium

INDEX OF SUBSTANCES RESISTANT TO DEGRADATION

The following substances proved to be resistant to degradation under the conditions of the test. As light was excluded, it is emphasised that some of the listed substances may be readily degradable under the influence of light.

Acetazolamide	Benzoic acid
Acriflavinium chloride	Benzyl benzoate

Ajmaline	Betamethasone
Allopurinol	Betamethasone valerate
Aluminium diacetate	Bupivacaine hydrochloride
Aluminium hydroxide	Busulfan
Amikacin	
Amiloride hydrochloride	Caffeine
Aminocaproic acid	Carbamazepine
Aminophenazone	Cetrimide
Amobarbital	Cetylpyridinium chloride
Amodiaquine hydrochloride	Charcoal,activated
Atropine sulphate	Chloramphenicol
Azathioprine	Chloramphenicol palmitate
	Chlorhexidine diacetate
	Chlorhexidine dihydrochloride
Barbital	Chloroquine phosphate
Barium sulphate	Chlorothiazide
Beclometasone dipropionate	Chlorproguanil hydrochloride
Benzocaine	Chlortalidone
Clofazimine	Iodine
Clofibrate	Isoniazid
Clomifene citrate	
Codeine monohydrate	Lactic acid
Colchicine	Lactose
Cyanocobalamin	Levodopa
	Levonorgesterol
Dexamethasone	Lidocaine
Dexamethasone acetate	Lindane
Diazepam	Lithium carbonate
Diazoxide	Lobeline hydrochloride
Dicoumarol	
Diethylstilbestrol	Magnesium chloride
Digitoxin	Magnesium oxide heavy
Digoxin	
Diloxanide furoate	Magnesium oxide light
Dimercaprol	Mannitol
Diphenhydramine hydrochloride	Mebendazole
Disodium edetate	Mepacrine hydrochloride
Dopamine hydrochloride	Meprobamate
	Methyldopa
Edrophonium chloride	Methyltestosterone
Ephedrine hydrochloride	Methylthiouracil
Eryhromycin	Metoclopramide hydrochloride
Eryhromycin ethylsuccinate	Metronidazole
Erythromycin stearate	Miconazole nitrate
Ethambutol hydrochloride	Morphine hydrochloride
Ehinylestradiol	
Etynodiol diacetate	Neostigmine bromide
	Neostigmine metilsulphate
Fludrocortisone	Niclosamide
Fludrocortisone acetate	Nicotinamide
Fluorescein sodium	Nicotinic acid
Fluorouracil	Nifurtimox
Folic acid	Nikethamide
Furosemide	Niridazole
	Nitrofurantoin
Glibenclamide	Norethisterone
Glucose	Norethisterone acetate
Griseofulvin	
	Papaverine hydrochloride
Haloperidol	Paracetamol
Halothane	Pentamidine isetionate
Hexachlorophene	Pentetrazol
Hexobarbital	Phenacetin
Homatropine hydrobromide	Phenobarbital
Hydrochlorothiazide	Phenolphthalein
Hydrocortisone	Phentolamine hydrochloride
Hydrocortisone acetate	Phenytoin
Ibuprofen	
Indometacin	Phenytoin sodium
Physostigmine salicylate	Sodium cromoglicate
Phytomenadione	Sodium fluoride
Piperazine adipate	Sodium hydrogen carbonate
Piperazine citrate	Sodium metaperiodate
Potassium bromide	Sodium nitroprusside
Potassium chloride	Sodium salicylate

Potassium iodide	Sodium thiosulphate
Prednisolone	Spironolactone
Prednisolone acetate	Streptomycin sulphate
Primaquine diphosphate	Sucrose
Probenecid	Sulfadiazine
Progesterone	Sulfadimidine
Proguanil hydrochloride	Sulfadoxin
Propanolol hydrichloride	Sulfamethoxazole
Propylthiouracil	Sulfamethoxypyridazine
Protionamide	Suramin sodium
Pyrazinamide	
Pyridostigmine bromide	Testosterone enantate
Pyrimethamine	Testosterone propionate
	Theobromine
Quinidine sulphate	Theophylline
Quinine dihydrochloride	Thioacetazone
Quinine sulphate	Thiabendazole
	Triamterene
Reserpine	Trihexyphenidyl hydrochloride
Riboflavin	Trimethadione
Rifampicin	Trimethoprim
	Tubocurarine chloride
Salazosulphapyridine	
Salicylic acid	Zinc oxide
Sodium bromide	Zinc undecylenate
Sodium chloride	

[**Close**]