

Guidance for Industry

Drug Stability Guidelines

(This version of the guidance replaces the version that was made available in December 1990. This guidance document has been revised to correct the contact information, address formatting issues and to add missing text linked to the table of contents.)

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**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Veterinary Medicine (CVM)
December 9, 2008**

Table of Contents

I.	INTRODUCTION.....	1
II.	BACKGROUND	1
III.	GENERAL CONSIDERATIONS	2
	A. PROTOCOLS	2
	B. GENERAL STABILITY CONSIDERATIONS.....	2
	1. Definition of Active Ingredient.....	2
	2. Strength (Potency)	3
	3. Drug Preparation.....	3

4.	Chemical and Physical Properties.....	4
5.	Added Substances	4
6.	Product Changes	4
7.	Correlation with Efficacy and Toxicity Studies.....	4
8.	Degradation Products.....	5
9.	Product Stability Parameters.....	5
C.	STORAGE CONDITIONS	5
1.	Shelf-Life Duration of Studies.....	5
2.	Expiration Dates.....	5
3.	Temperature	7
4.	Environmental Factors	8
5.	Special Labeling Restrictions	8
D.	CONTAINERS.....	8
1.	Intended Market Container	9
2.	Container Material Integrity	9
3.	Containers for Liquids: Special Considerations	9
4.	Physical Observations.....	9
5.	Sealed Containers.....	9
6.	Adhesive/Glue.....	10
7.	Container Changes	10
E.	STABILITY SAMPLES.....	10
1.	Samples	10
2.	Sampling Plan	11
3.	Handling and Analysis of Samples	11
F.	STABILITY SCHEDULE.....	11
1.	General.....	11
2.	Test Schedule Information.....	13
3.	Table of Suggested Test Schedules.....	16
G.	ANALYTICAL METHODS	18
1.	Quality Control/Release Methods.....	18
2.	Method Attributes	18
3.	Method Controls and Conditions	20
4.	Standards Curves	20
5.	Stability Method References.....	20
H.	STATISTICAL EVALUATION.....	23
1.	Design Considerations	23
2.	Data Analysis.....	23
3.	Expiration Date Determination.....	23
I.	REPORTING OF DATA	24
J.	STABILITY STUDY COMMITMENTS	25
1.	Initial Study Commitments	25
2.	Product/Container Changes/Alternate Drug Substance Suppliers.....	26
3.	Analysis of Distribution Samples	26
4.	Post-Approval Studies	26
K.	STABILITY STUDY COMMITMENT FORMAT.....	26
1.	Samples of Testing.....	26

2.	Control Tests.....	27
3.	Container.....	27
4.	Product Storage Conditions	27
5.	Frequency or Interval of Testing.....	27
6.	Result Reporting	27
7.	Withdrawal Provisions.....	27
IV.	SPECIFIC CONSIDERATIONS	28
A.	PHARMACEUTICAL DOSAGE FORMS	28
B.	STERILE PREPARATIONS.....	29
C.	TYPE A, B, AND C MEDICATED PRODUCTS	30
1.	Expiration Dating Requirements.....	30
2.	Study Temperature and Length.....	31
3.	Product Composition	32
4.	Lots for Stability Study.....	33
5.	Testing Levels.....	33
6.	Pelleted Products.....	33
7.	Moisture Content	34
8.	Test Results.....	34
9.	Additional Studies.....	34
10.	Pilot vs. Production Samples	35
D.	TYPE B AND C MEDICATED LIQUID FEED SUPPLEMENTS.....	35
1.	Protocols	36
2.	Stability Test Information.....	36
3.	Types of Stability Testing.....	38
4.	Stability Testing Studies	38
5.	Recommended Labeling	41
E.	MEDICATED BLOCKS.....	43
1.	Stability Study.....	43
2.	Label Statement for Usage.....	44
F.	SOLUBLE POWDERS AND DRINKING WATER.....	44
1.	Soluble Powders.....	44
2.	Drinking Water	45
G.	ORAL DRENCHES.....	45
H.	MILK REPLACERS	46
I.	MASTITIS PREPARATIONS	46
J.	SUSTAINED – RELEASE PRODUCTS	47
K.	MICROENCAPSULATED PRODUCTS.....	47
L.	VAT DIPS.....	47
M.	rDNA PRODUCTS	47
N.	DRUG SUBSTANCES.....	48

Guidance for Industry

Drug Stability Guidelines

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

The guideline is to be used as an aid in designing and conducting studies to establish drug stability in support of original, abbreviated or supplements to new animal drug applications (NADAs/ANADAs). The guideline will provide a framework within which stability studies can be conducted to provide meaningful and sufficient data. The concept of the guidelines is applicable to studies on drug substances and the actual dosage form. The guideline is not intended to restrict experimentation. The guideline applies to pharmaceutical dosage forms and medicated feed products.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Section 512(b) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 360b) establishes the requirements for new animal drug approval. 21 CFR 514.1 specifies the proper form and the information required to be submitted. Included is a requirement under section 514.1(b)(5)(x) that an applicant submit data from stability studies completed as well as information about studies that are underway to substantiate the request for a specific expiration date and provide information on the stability of the drug products.

CGMP regulations under 21 CFR Part 200 also require stability testing for pharmaceutical dosage forms (21 CFR 211) and Type A Medicated Articles (medicated premixes) (21 CFR 226). This guideline can be used as an aid to conduct the required stability testing.

The agency advises that this final guideline represents its current position on the development of stability studies to meet the requirements of the submission of original or abbreviated new

animal drug applications and the corresponding CGMP regulations. The guideline may be useful to manufacturers of new animal drug products. A person may follow the guideline or may choose to use alternate procedures even though they are not provided for in the guideline. If a person chooses to use alternate procedures, that person may wish to discuss the matter further with the agency to prevent an expenditure of money and effort on activities that may later be determined to be unacceptable by FDA. This guideline does not bind the agency, and it does not create or confer any rights, privileges, or benefits for or on any person.

III. GENERAL CONSIDERATIONS

A. PROTOCOLS

Prior to the submission of an original or supplemental NADA, an applicant may wish to submit a stability protocol for comment before committing to studies that will become a permanent part of the NADA.

The protocol should contain an outline of the proposed plan to be used in generating stability data. The protocol should describe the type of product being tested, sampling process, duration and frequency of testing, number of samples and replicates per time interval, storage conditions (length of storage, type of storage, temperatures and packaging), methods of analysis (description or reference of published methods) with accompanying support data, if available, and other tests. The information listed in these guidelines should be incorporated as appropriate in the development of a plan.

The Center's review scientists will evaluate and comment on the proposed protocols or assist an applicant (upon request) in the design of a study.

It should be noted that the Center for Veterinary Medicine does not approve protocols.

Applicants or drug firms proposing to conduct stability studies should refer to the following texts:

- "Chemical Stability of Pharmaceuticals" by K. Connors, G. Amidon and L. Kennon, John Wiley & Sons (1979).
and
- "Formulation of Veterinary Dosage Forms", vol. 17, Drugs and The Pharmaceutical Sciences, Blodinger, J., Marcel Dekker Inc., NY. (1983). Chapter 5.

These texts provide information on the various aspects of establishing a stability program.

B. GENERAL STABILITY CONSIDERATIONS

1. Definition of Active Ingredient

The active ingredient of an animal drug preparation is defined as that chemical whose biological, physiological, pharmacological, or chemical activities are claimed on the label to be beneficial for animals in normal or pathological conditions (diagnosis, prognosis, treatment, prophylaxis, therapy) or for animal production.

2. Strength (Potency)

The strength of a drug substance may be its concentration (quantity of the drug per unit measure), its potency, or both. The potency of a drug is a measurable (quantitative) extent of the biological, physiological, pharmacological, or chemical activities of the drug per unit weight or volume of the drug preparation.

Drug preparations are considered stable if the active ingredient can maintain its strength at the level specified on the label for the maximum anticipated shelf-life (the time period from the date of manufacture until administration to the animal) under environmental conditions likely to be encountered in actual use. However, few, if any, drug preparations maintain their full label-claimed strength under specified conditions. Therefore, allowances are made for some unavoidable deviations from drug levels declared on the label by designating specific limits for tolerable deviations.

A drug product is considered unstable when the drug substance (active ingredient) loses sufficient potency to adversely affect the safety or efficacy of the drug or falls outside labeled specifications as shown by stability-indicating methods.

To properly evaluate the stability of a drug product, it is essential to determine the storage conditions under which the drug strength can be maintained in order to provide a safe and efficacious drug product.

As a guide in determining drug strength in pharmaceutical dosage forms, the following is recognized by the scientific community:

- "Although there are exceptions, 90% of the labeled potency is generally recognized as the minimum acceptable potency level."¹

3. Drug Preparation

The active ingredient should be formulated in any drug preparation at 100% of label claim. An overage of the active ingredient may be permitted in a product should the need exist. All overages should be

¹ *Remington's Pharmaceutical Sciences*, Sixteenth Edition, Pg. 284 (1985).

justified. The assay limits must account for the overage. The overage should not exceed the limits of 5% for antibiotics and 3% for nonantibiotic chemicals as established by the Center for Veterinary Medicine.

4. Chemical and Physical Properties

Strength is not the only criterion of drug product stability. Maintenance of various chemical and physical properties to preserve the effectiveness and safety of the drug is also important. Properties, such as physical appearance, crystalline form, particle size, solubility, disintegration rate, pH, sterility, viscosity, palatability (taste and odor), may be stability related and thus require testing and the setting of specific storage conditions and limits. In addition, tests may also be needed to determine the absence or presence of harmful degradation products.

5. Added Substances

Stability data on substances that are added to a drug preparation to enhance its stability, usefulness, physical or chemical properties or as an aid in manufacturing may be required. The type of substance(s) used, its purpose, and its relationship to the active drug ingredient(s) and total drug preparation will determine if testing for the substance is required. Examples of added substances that may commonly be used are antioxidants, antibacterials, absorbants (bentonite), etc.

6. Product Changes

Changes made in the composition (formulation) or dosage form of the original or succeeding product(s) present a new drug product and will require generation of new stability data. Data requirements will depend on the nature and degree of change.

Any change requires an evaluation as to the effect on the stability of the products.

7. Correlation with Efficacy and Toxicity Studies

Stability studies supporting an application should be performed on the drug preparation in its final formulation whose efficacy and safety has been demonstrated. Any change made in an approved preparation requires consideration of the effects on the efficacy and safety of the "changed" drug product.

8. Degradation Products

Degradation products that occur during storage (under shelf-life testing) should be identified. These products should be thoroughly investigated and evaluated for safety and toxicology purposes. The presence of degradation products may require additional safety and efficacy studies.

9. Product Stability Parameters

The established regulatory registration (NADA or NDA) specifications or Compendial standards are to be used for determining the stability of the products. There can be only one set of standards. Samples of products (from production lots) on stability should be representative of those in the market place. Expiration dating is based on the ability of the product to be measured over a certain period of time against the established specifications or standards.

C. STORAGE CONDITIONS

In setting up the environmental conditions under which the stability of the drug preparation will be studied, the end use of the product should be kept in mind. Consideration should be given to simulating conditions to which the preparation will be exposed during shelf-life and expiration periods. These conditions should include stock storage and transportation conditions under proposed label directions.

1. Shelf-Life Duration of Studies

Stability studies should be designed to provide enough useful information to determine the anticipated shelf-life of a drug product, when stored under conditions set forth on the labeling.

The duration of stability studies should extend at least to the usual shelf-life for that type of product or beyond the recall specification limits, whichever is shorter.

Shelf-life is defined as the time period from the date of manufacture of the product until it is administered to the animal.

2. Expiration Dates

The applicant should propose a tentative expiration date on the basis of available stability data. This expiration date may be based on analysis of pilot-lot data.

The accumulation of stability data from production lot samples will justify any adjustment (reduction, extension or removal) of the proposed tentative

expiration date. The requirement for expiration dates is found under 21 CFR 211.137 and 211.166 for pharmaceutical dosage forms and 226.58(d) for Type A medicated articles of the good manufacturing practice regulations.

In addition, 21 CFR 514.1(b)(5)(x) lists the basic requirement of an expiration date for all veterinary products:

- a. Pharmaceutical Dosage Forms:
Expiration dates are required.
- b. Medicated Feed Products:
 - i. Premixes [Type A medicated articles]
Expiration dates are required.
 - ii. Supplements/Intermediates [Type B medicated products]
The need for an expiration date will be determined on a case-by-case basis (depending on the proposed uses, etc.).
 - iii. Complete Feeds [Type C medicated products]
The need for an expiration date will be determined on available stability data submitted and the proposed uses.

Experience indicates that the following periods are the maximum time periods commonly used in determining product expiration periods:

<u>PRODUCT TYPE</u>	<u>MAX. TIME PERIOD</u>
Dosage forms:	5 years
Implants, injectables, tablets, capsules, soluble powders, etc.	
Medicated Products:	
Liquid feed supplements	60 days ¹
Type A Medicated Articles [Premixes]	*
Type B Medicated Feeds	**
Type C Medicated Feeds [Finished Feeds]	*
Type C Medicated Feeds [Blocks]	180 days ²
Medicated drinking water	Label Directions ³

Each dosage form or medicated feed preparation will have its own unique shelf-life.

NOTE: The expiration date period should begin at the time of manufacture of the lot.

¹ Shelf-life figures less than or greater than this figure may be proposed or be necessary. Based on the stability data presented and the proposed use, acceptability will be determined on a case by case basis for the product.

² The shelf-life of blocks should be determined according to label directions, consumption data, range (open field) stability studies combined with the warehouse shelf-life (180 days).

³ The shelf-life of medicated drinking water should be determined by stability studies based on label directions for use. (See section F for additional information.)

* Sufficient historical data/information is not available to list a maximum time period for this type product. Expiration date assignment will be based on data submitted.

** Depending on type (intermediate, supplement, etc.), the level and/or proposed use of this product, the time period can fall under the Type A (premix) or Type C (medicated feed) categories. The need for an expiration date will be determined on a case-by-case basis.

3. Temperature

It is recommended that in order to study the stability profile of the active ingredient(s) and drug preparation, samples should be stored at temperatures of 25°C and 37°-40°C, although in some instances, higher or lower temperatures may be required.

Those preparations labeled for storage at freezing or refrigerator conditions are to be studied at these temperatures.

On occasion, studies at elevated temperatures, i.e., greater than 40°C may be necessary.

Non-isothermal studies may also be utilized where advisable or considered necessary to determine a tentative expiration date.

Comparison of data obtained at different storage temperatures provides useful information about the temperature-drug relationship and the need for any special storage conditions.

4. Environmental Factors

The following conditions are some of the factors that should be considered in determining stability during storage:

- a. Effect of exposure to extremes of temperature.
- b. Effect of exposure to air, sunlight, ultraviolet light and other artificial light.
- c. Effect of exposure to humidity (normal or exaggerated conditions).

5. Special Labeling Restrictions

Drug products that may be expected to be exposed to extremes of temperature, humidity, air, light, etc., may require special label restrictions. The restrictions should be practical and such that they can reasonably be expected to be followed under actual conditions.

All recommended restrictions must be supported by appropriate data.

D. CONTAINERS

Regulation 21 CFR 211.94 of the current good manufacturing practice (CGMP) regulations for pharmaceutical dosage forms provides information that is to be used when considering containers for drug products. The regulation is published below:

§211.94 Drug product containers and closures.

- (a) Drug product containers and closures shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug beyond the official or established requirements.
- (b) Container closure systems shall provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the drug product.
- (c) Drug product containers and closures shall be clean and, where indicated by the nature of the drug, sterilized and processed to remove pyrogenic properties to assure that they are suitable for their intended use.
- (d) Standards or specifications, methods of testing, and, where indicated, methods of cleaning, sterilizing, and processing to remove

pyrogenic properties shall be written and followed for drug product containers and closures.

Even though this regulation is for pharmaceutical dosage forms, it is used as a guide for containers for all other veterinary products, e.g., Type A medicated articles, complete feeds, blocks, etc. The text and concepts embodied in the regulation can be applied to all types of packaging for veterinary products. It is used in assessing the usefulness of the proposed container and the stability of the product in the proposed container. It should be noted that sections (c) and (d) of the above regulation are not applicable for all veterinary product packages.

1. Intended Market Container

In order to demonstrate stability of the drug product under actual or simulated storage conditions, the product must be studied in its intended market container(s). This is required under 21 CFR 211.166 (a)(4).

2. Container Material Integrity

The container should be capable of preventing physical dissipation of the drug substance or other excipients by means of evaporation, permeation, absorption, adsorption or leaching through the container wall. Container materials should not interact with the product.

In some instances, the use of containers smaller in volume than the market container but identical in composition and construction may be permitted. Proper justification must be provided.

3. Containers for Liquids: Special Considerations

Container/closure systems which hold liquid products - injections, solutions, suspensions - should be stored in both upright and inverted positions. This type of storage is necessary to provide information on any possible reaction between the product and the cap, seal, stopper, etc. Tests should be performed for integrity of seal, torque fit (if necessary), leaching from liner or closure, leaking, etc.

4. Physical Observations

Physical observations of the container and contents should always be made and reported during any stability testing period. Tests should be conducted as needed to confirm any unusual findings and be reported.

5. Sealed Containers

Products that are hermetically sealed should be tested for integrity of seal.

6. Adhesive/Glue

High temperature studies may be needed to study the stress of adhesive properties of any glue used.

7. Container Changes

The following information is applicable to pharmaceutical dosage forms and medicated feed products as appropriate.

a. Container Material Change

A change in the type of container material used in the composition of the container (unless it is considered comparable, i.e., in the same generic chemical class to that as approved), will require new stability studies to be conducted with the drug product.

b. Container Size/Shape Change

A change in the size or shape of the original container may not necessitate the initiation of a new stability study. The decision will be made at the time of the review of the NADA supplement.

c. Introduction of New Containers or Closure Systems

Whenever new containers or closure systems are introduced for use with a product, the first three (3) production lots of product using the new container or closure system should be placed into study using the approved ongoing stability program.

E. STABILITY SAMPLES

1. Samples

Samples from production-size batches are preferred and should be used for stability studies. These type samples provide for approximate actual use conditions. The applicant should use real world conditions as much as possible. If pilot scale samples are used, this fact should be reported. Laboratory scale samples provide for optimum control of all factors. Therefore, it should be kept in mind that changes may be needed in specifications once the drug is approved for use and the "real" or "actual" use situations are monitored and evaluated. Such changes may be provided by the applicant or be requested by the Agency.

2. Sampling Plan

A description of the sampling plan should be submitted to show how samples are representative of the lot or batch. In addition, the frequency of sampling and the number of samples taken per time period should be reported. Certain information on which to make these decisions should be given, for example, the variability of the assay method at the concentrations being determined should be considered. Greater variability may necessitate an increase in the number of samples needed at each time period.

3. Handling and Analysis of Samples

To establish the initial data point, samples should be analyzed as soon as possible after they are manufactured. The same day is highly desirable. This is recommended in order to make sound and valid conclusions about the stability of the active drug ingredient(s) and the preparation. If the initial analysis cannot be performed on the same day, the samples should be placed in moisture-proof, air-tight containers and sealed with as little air as possible inside. They should be stored at 0°F or at some temperature chosen to reduce the chance of degradation, mold growth and chemical action.

Storage of frozen samples for an extended period of time should be avoided. Those preparations that cannot be stored at freezing temperatures should be analyzed as soon as possible to establish an initial analysis point and then be placed in their appropriate stability testing environment. Samples that are shipped to sites other than the manufacturing site for stability testing should be properly packaged and labeled. These samples should be tested upon receipt prior to their introduction into the respective stability program. An initial analysis should be conducted as soon as possible, at release or upon receipt.

F. STABILITY SCHEDULE

Suggested Schedules for conducting Stability Studies

1. General

In general, a schedule for conducting stability testing should be established which represents the conditions under which the preparation will most likely be stored. The schedule in conjunction with a stability commitment should be designed to establish a stability profile for the product.

a. Pre-Approval Studies

Prior to approval of the drug product for use, the applicant should propose a stability schedule. The schedule should be submitted with the stability commitment for review.

Acceptability of the schedule and commitment will be based on the information received, past history of the drug substance, related drug preparation(s), storage conditions and accompanying commitments. Discussions with the applicant will be held when necessary.

The information may be submitted during the investigational drug stage as a protocol for review or with the submission of a new animal drug application.

At least 3 lots of product of a typical batch size should be tested for stability.

b. Post-Approval Studies

Post approval commitments and studies should be designed to insure and verify the adequacy of pre-approval data and that the change from pilot to production lot has not introduced any unknown variable or been influenced by any unforeseen problems.

After sufficient stability information has been accumulated, revised commitments may be submitted to adjust the suggested schedule.

c. Stability Tests

Under any particular schedule, all the pertinent stability tests - physical, chemical or microbiological - which have been designed for the study must be conducted. Results are to be reported as per the stability reporting commitment.

d. Reformulated Products

Reformulated products are considered as new products and should, therefore, be subjected to the ongoing original product stability schedule and commitment.

e. Accelerated Temperature Studies

Accelerated temperature studies should be conducted when necessary to provide information for stability prediction or tentative expiration date period.

2. Test Schedule Information

The information discussed in the section below is related to the table of suggested schedule.

a. Temperatures

i. Room Temperature

1. Pharmaceutical Dosage Forms

All pharmaceutical dosage forms should be studied at 25°C (77°F) which is considered the normal room temperature. If another "normal room" temperature is studied or required for storage, the study should then follow the schedule at that temperature.

2. Feed Preparations

Feed preparations should be studied under the following schedules:

a. Type A Medicated Articles
(Medicated Premixes)

Type A medicated articles should be studied at room temperature (25°F or 77°F) under the same schedule intervals as Pharmaceutical Dosage Forms.

b. Type B & C Medicated Products

Type B and C medicated feed products should be studied at ambient temperatures. (Ambient temperatures are those that actually occur during a certain time period.)

Type B products should be studied for the appropriate period depending upon what category it is judged to belong, e.g., as an intermediate premix or a supplement.

Type C products should be tested as follows:
Complete, finished feed - 0(initial), 1, 2, 3
mos.

Blocks - 0(initial), 2, 4, 6 mos.
Liquid feeds (field storage) - 0(initial), 2, 4,
6, 8 weeks.

NOTE: See section F for the definition of
ambient temperatures.

ii. Elevated Temperatures

Simultaneous to the normal room temperature stability study, a study should be run for a shorter period of time at a higher temperature.

1. Pharmaceutical Dosage Forms

The period should be for at least one year at 37° to 40°C. See "Table of Suggested Test Schedule" for the appropriate schedule.

2. Type A Medicated Articles (medicated premixes)

The period should extend for at least 6 months at 37° to 40°C. "Table of Suggested Test Schedule" for the appropriate schedule.

3. Type B Medicated Feed Products

Type B products should be studied for the appropriate period depending upon what category it is judged to belong, e.g., as an intermediate premix or a supplement.

4. Type C Medicated Feed products

The period should be studied at 37° to 40°C.

Complete, finished feeds - 1 month

Blocks - up to 6 months

Liquid feeds - 8 weeks

Periods less than stated times should be justified.

Under actual real life environmental conditions, the higher temperatures are not expected to exist for long periods. However, in order to study the stress placed on the

preparation by possible higher temperatures data from elevated studies must be provided.

iii. Refrigeration

Those preparations that may require refrigeration either in the intact, unopened container or after opening or after reconstitution should be studied within the schedule for the length of anticipated storage period or expiration date. The study should include tests on unused portions in opened containers after initial use, when appropriate. Preparations that may come under this category are liquids, solutions, injections, suspensions, creams, ointments, pastes, and some solid dosage forms, e.g., powders, suppositories and reconstituted solutions.

vi. Freezing

All liquid preparations - injections, solutions, suspensions, and semi-solid preparations (creams, ointments and pastes), medicated liquid feeds, etc. - should be subjected to a short term stability study at freezing temperatures. This short term period should cover at least 7 days.

1. Physical observations should be made daily to determine if precipitates or other abnormal occurrences are evident.
2. If the preparation is frozen, procedures for thawing should be recommended.
3. If a precipitate remains after thawing, the precipitate should be identified. The toxicity and safety of the identified precipitate should be determined, if necessary. Procedures for dissolving the precipitate, if possible, should be recommended. Proper product labeling directions should be provided.
4. If separation of layers in suspensions occur, procedures for thawing frozen material and reconstituting the product to its original state, should be recommended.

At the end of the freeze test period, the normal stability tests should be conducted to insure that the product has maintained its standards and degradation has not occurred.

If the results of the above studies indicate any abnormalities, proper warnings may need to be appended to the label and be placed in the insert.

v. Ambient Temperatures

Certain types of products may need to be studied under natural environmental conditions. The existing weather conditions should be reported. Temperatures (minimum and maximum) should be reported at the time of sampling and testing. Products that may be studied under these conditions are medicated feeds, blocks or liquid feeds which are used outdoors and, therefore, are expected to be exposed to natural, existing temperatures.

b. Special Humidity Considerations

Those preparations requiring a special humidity environment should include that factor (amount of humidity) with the temperature schedule under study.

3. Table of Suggested Test Schedules

a. Solid Dosage Forms Including Medicated Feed Products

i. All products should be subjected to both room temperature and elevated temperature studies (length depending on the proposed expiration date).

1. Room Temperature: 25°C (ca 77°F); or other²

Proposed Expiration Date	Test Schedule
6 months	0 (Initial),2,4,6 mos.
1 year	0 (Initial),3,6,9,12 mos.
18 months	0 (Initial),3,6,9,12,18 mos.
2 years	0 (Initial),3,6,9,12,18,24 mos.
3 years	0 (Initial),3,6,9,12,18,24,36 mos.
4 years	0 (Initial),3,6,9,12,18,24,36,48 mos.
5 years	0 (Initial),3,6,9,12,18,24,36,48,60 mos.

² When a temperature other than that specified above is to be used, it should be specified in the protocol or study.

2. Elevated Temperatures: 37-40°C (98-104°F)

Proposed Expiration Date	Test Schedule
6 months	0 (Initial),2,4,6 mos.
1 year or greater	0 (Initial),3,6,9,12 mos.

3. Ambient Temperatures

Actual temperature existing at location of stored product. (This level does not represent "controlled" temperatures.)

- ii.* Those products requiring refrigeration must be subjected to the appropriate study at the respective temperature station.

Normal refrigeration temperatures: 2°-8° (36° - 46°F)

Schedule and length of anticipated storage period (expiration date) under these conditions will depend on nature of the product, active ingredient and/or other related factors.

Note: If possible, samples should be studied at both temperature settings.

b. Liquid and Semi-Solid Type Products

In addition to the schedules in a. (above), all liquid and semi-solid products (e.g. pastes, ointments, liquid feeds, etc.), should be subjected to a freeze-thaw-freeze cycle study.

Freezing temperature should be 0°C (32°F) or below.

Test schedule: 0(initial).....7 days

c. Reconstituted Products

Time element and schedule will depend upon nature of product, active ingredient, proposed expiration date and/or other related factors.

Example: A powder dissolved in a solvent to be held for 14 days should be tested at the recommended storage temperature (room, elevated and/or refrigerated temperature stations) according to the following schedule:

0(initial),3,7,11,14 days.

NOTE: Extension of the period schedule may be necessary and will depend on review of the data obtained. A significant loss in potency is an example that may cause an extension of the time schedule. Other examples may include, appearance of degradation products, aberrant physical observations, etc. The decision to extend the period will be made on the evaluation of data submitted to the Center or by the firm on its own initiative.

G. ANALYTICAL METHODS

A key factor in a stability study is the use of an analytical method which will provide meaningful and reliable data. In all cases, the method should be capable of providing proper information for each test conducted.

Stability assay methods should be sufficiently specific to differentiate between the unaltered drug and any possible degradation products. The method should be described in detail.

All assay methods should be supported by accuracy and precision information and be properly validated.

All analyses should be conducted in replicate, preferably in duplicate. The raw data should be reported.

1. Quality Control/Release Methods

Official (USP, NF, AOAC, et. al.) or other control methods may be used for assaying the finished products. These same methods or in-house quality control tests may serve as stability methods if they can be shown to be stability-indicating.

In any case, it is the responsibility of the applicant to provide sufficient data to demonstrate the method's suitability as stability-indicating for the product being tested.

2. Method Attributes

A stability-indicating method should address the following attributes: accuracy, precision, specificity and limit of detection. The mechanisms for determining these attributes can be found in appropriate textbooks and the scientific literature.

a. Accuracy

The accuracy of an assay method is a statistical measurement which relates to the difference between the average test results and the true value when the latter is known.

At a minimum, the average mean recovery of the active ingredient(s) from the preparation should be determined at the label claim (assumed to be 100%) and at two additional points, each bracketing the label claim irrespective of the presence of an allowable manufacturing overage.

The percent recovery from fortified (spiked) samples or synthetic mixtures containing a known amount of drug is the usual way of measuring accuracy.

b. Precision

Precision involves the statistical measurement that is related to the repeatability of the method. Precision is measured by the standard deviation or coefficient of variation of the method at the levels of interest.

c. Specificity

The method should be specific enough to determine the active ingredient(s) as the intact molecule in the presence of other substances, such as: closely related drugs, intermediates, impurities, degradation or by-products, or the drug preparation excipients that could reasonably be expected to mask or simulate the analytical behavior of the ingredient.

As part of the specificity test for a stability-indicating method, the product should be tested with acid and base to determine if decomposition occurs with the active ingredient. Decomposition testing with sunlight or artificial light should also be performed.

In some cases, confirmatory techniques may be necessary to determine the specificity of a method.

Copies of actual spectra, chromatograms, photographs of TLC plates or other data/information should be submitted to substantiate this attribute.

d. Limit of Detection

The method must be able to respond to the least amount of the chemical under analysis.

3. Method Controls and Conditions

a. Method Blanks

i. Control (Reagent) Blank

A control (or reagent) blank should always be run whenever the method is performed unless the method does not require one, such as, with the use of an internal standard. A method control blank is a solution made of solvents used in the method prepared according to the method procedures. This control is necessary to assure proper validation and to show noninterference of the sample with the method solvents (reagents), proper functioning of the equipment, and that proper analytical techniques are being exercised.

ii. Sample Blank

When a sample blank is used, it should consist of all excipients of the drug product less the active ingredient. This sample blank should normally be used only during product and method development stages.

Sample blanks are not acceptable for a product release of regulatory or stability testing method.

b. Method Conditions

Parameters (or conditions) under which the method is conducted should be properly documented and reported.

4. Standards Curves

For those methods requiring the use of a standard curve, the curve should be prepared on the day the method is run. At least 3 points must be plotted to provide meaningful data and interpretation.

5. Stability Method References

The following articles may be referenced as guides for analytical method validation:

- Guidelines for Assay Validation
Pharmaceutical Technology, March 1982, pg. 66
- Submitting HPLC methods to the compendia and regulatory agencies
Pharmaceutical Technology, September 1982, pg. 120
- Practical applications of cGMPs to gas and high-performance liquid chromatographic systems
Pharmaceutical Technology, March, 1984, pg. 81
- Validating alternate laboratory assay methods
Pharmaceutical Technology, May 1979, pg. 60
- Standard Additions: Uses and limitations in spectrophotometric analysis
American Laboratory, July 1977, pg. 21
- GMP - method validation procedures in an OTC firm
Pharmaceutical Technology, August 1980, pg. 45
- Stability of Pharmaceutical Products
Remington's Pharmaceutical Sciences, 1985
- Stability of Pharmaceuticals
J. Pharm. Sci. 67, 443, 1978
- Stability Studies of Veterinary Formulations
Formulations of Veterinary Dosage Forms, J. Blodinger, Marcel Dekker, 1983, Chapter 5

NOTE: The above list is not meant to be all inclusive. Articles are constantly being made available for scientific use. The above articles are referenced here only as an aid or guide for use in developing stability methods and conducting the validation process.

The format for the presentation of analytical methods should be one that is clear and contains all necessary information. The following format is suggested:

TITLE OF METHOD

I. SCOPE/PRINCIPLE OF METHOD

This section should briefly describe the physical process and chemical principle of the method.

II. APPARATUS

This section should provide all information for the use of the equipment or other apparatus necessary to conduct all aspects of the method.

III. REAGENTS

This section should list all the reagents and their preparation (where necessary) used to conduct the method.

IV. PROCEDURE

This section should contain all information applicable and relative to the sample, standard and blank preparation (extraction, clean-up, dilution, etc.,) instrument parameters, determination and calculations.

- (a) Sample Preparation
 - (i) Extraction
 - (ii) Clean-up
 - (iii) Dilution
 - (iv) Other
- (b) Standard Preparation
 - (i) Extraction
 - (ii) Clean-up
 - (iii) Dilution
 - (iv) Other
- (c) Blank (Reagent) Preparation
- (d) Instrument Operating Parameters
 - (i) Instrument
 - (ii) Ancillary units
 - (iii) Operating conditions
 - Columns
 - Temperatures
 - Special calibration
 - Other
- (e) Determinative Step
- (f) Calculations (all dilution factors and calculation parameters should be clearly explained.)
- (g) Raw data; Summary of results
- (h) Chromatograms, spectra, etc.
- (i) System Suitability information, if necessary

V. VALIDATION INFORMATION

- (a) Accuracy
- (b) Precision
- (c) Specificity
- (d) Sensitivity
- (e) Reproducibility
- (f) Ruggedness

VI. OTHER RELATED INFORMATION

This section should contain information to ensure the method is being properly controlled

H. STATISTICAL EVALUATION

It is the responsibility of the applicant to design the stability study and then apply the proper statistical techniques. The information listed below includes items felt necessary and important to the stability study. The type or depth of statistical approach to be used should be sufficient to accurately define and interpret the results obtained.

1. Design Considerations

The first point to be examined in the design of a stability study is the population to which inference is to be made. This means, for example, that if the stability of different batches (or lots) is to be inferred, then samples from more than one batch must be put on test. Furthermore, research or pilot batches should be comparable to production batches. The sources of variation should be identified and quantified in order to estimate the number of batches, samples per batch, assays per sample, etc., needed in the study. These variance estimates should be made from preliminary studies or previous experience with the drug. Batches may be manufactured and assays measured at staggered intervals in order to minimize the [5~influence of day to day variations in the assay method.

2. Data Analysis

The data may be modeled using regression techniques, with "goodness of fit" tests used to assess the adequacy of the model. The expiration date is defined so that at least 90% of all samples will be above the stability limit (e.g., 90% of label claim) throughout the shelf-life of the drug. This expiration date will be determined from the fitted model and the estimated batch to batch and/or sample to sample variation.

Data should be presented in a form that is amendable to statistical analysis and readily understood by the reviewer. Statistical evaluations are strongly recommended. The procedures employed should be described or relevant references given. When appropriate, graphs and other visual aids may be provided.

3. Expiration Date Determination

The method for determining the expiration date should be described. References to Journals or text books are acceptable. Information described in *Journal of Pharmaceutical Sciences*, 65, 311, Feb. 1976 can

be used as a guide. There is no specific method that is accepted as the method of choice. Each applicant must provide the information needed.

I. REPORTING OF DATA

When reporting stability data, the following information should be included:

1. Name and type of product
2. Lot number and size of lot under test
3. Formulation

NOTE: For a medicated feed, report the formulation of base feed used as a diluent.

2. Label Claim
5. Conditions of storage
4. Type of container(s)
7. Analytical and Physical data:
 - a. Assay and identity tests
 - component (ingredient(s)) tested for.
 - individual data with appropriate units.
 - description of tests or references.
 - specifications (limits) - +% label claim.
 - sample of calculations, where necessary.
 - b. Other tests (pH, disintegration, etc.)
8. Statistical presentation, if available
9. Names and addresses of testing facilities

Spectra, chromatograms, charts, or other pertinent information should be submitted to support and clarify any submitted data. The applicant must make the determination when this information is necessary.

Those applicants utilizing computers may submit data in computer-readable form. Explanations should be presented along with the computer information to clarify the format, nomenclature, etc., used.

J. STABILITY STUDY COMMITMENTS

1. Initial Study Commitments

a. Purpose

Since stability data submitted as part of a new animal drug application are almost invariably based on laboratory or pilot-scale batches, the problems associated with the scale-up to full-size production batches must be considered. In order to demonstrate that the transition can be made from pilot-scale to full-scale production without encountering stability problems, a stability-testing protocol with corresponding commitments should be developed and submitted.

b. Protocol and Commitments

The protocol for a stability study with necessary commitments should include the following information:

- i.* The number and/or frequency of production batches to be placed in a continuing stability study.
- ii.* Description of the chemical, microbiological, and physical tests to be used to monitor the stability of the drug product.
- iii.* Description of the containers to be used.
- iv.* The proposed environmental and storage conditions under which the drug product will be studied and then marketed.
- v.* Frequency or intervals of testing.
- vi.* Frequency at which results will be reported.
- vii.* Provisions to test batches manufactured immediately before and after a production batch which is found to be out-of-specifications.
- viii.* Provisions for withdrawal from the market of any production batch found to be out-of-specifications and, if necessary, those batches immediately before and after the batch in question.

2. Product/Container Changes/Alternate Drug Substance Suppliers

Whenever changes in formulation (changes in drug concentration or inactive ingredients), use of new containers, alternate sources, etc., are made, the product manufactured under the new conditions should be placed into the ongoing approved stability study.

A commitment should specify all conditions relative to the new change and a statement to perform any additional studies needed for the changes in the application.

In most cases, the approved expiration date may be used. However, this will be determined at the time of the review of the supplemental submission and requested action.

3. Analysis of Distribution Samples

Although not mandatory, it may be desirable to obtain samples from distributed batches for stability testing. Ideally, these samples should be obtained from geographical areas which represent extremes of temperature and humidity.

It should be noted that the above voluntary activity does not relieve the applicant from the requirements for stability testing as established under cGMPs.

4. Post-Approval Studies

After approval, the sponsor may make a request to liberalize or remove storage condition restrictions, to adjust (extend, reduce or remove) an expiration dating period, remove or provide a storage temperature restriction, provide for use of a different container, or amend existing commitments. In these cases, adequate stability data should be presented to justify the request.

K. STABILITY STUDY COMMITMENT FORMAT

A commitment to assure stability of a product should specifically define the following items.

1. Samples of Testing

The first three (3) production lots should be tested followed by 3 to 10% of annual production lots (with a minimum of 1 lot per year).

The number and/or frequency of production batches to be placed on a continuing stability study should be based on a consideration of the anticipated annual production and known stability profile.

2. Control Tests

The chemical, microbiological, and physical tests to be used to monitor the stability of the drug product should be described.

Tests and methods must be appropriate and adequate for the study.

Assay methods must be stability-indicating, i.e., they must accurately differentiate between the intact drug molecule(s), any possible degradation products and product excipients. Methods must be adequately validated.

3. Container

The container to be used should be described.

The container and closure system should be those proposed for use in marketing the product.

4. Product Storage Conditions

Product storage conditions must specify type of storage, temperature and humidity conditions, light, etc. These conditions must be applicable to the drug product in the market container and label requirements.

5. Frequency or Interval of Testing

The schedule of testing samples relative to the proposed expiration date period at the recommended temperatures should be described.

6. Result Reporting

Prior to approval for marketing, all available data should be submitted with the original applications and any amendments. Post-approval data may be reported in the Drug Experience Report (DER) or in supplemental applications.

7. Withdrawal Provisions

Provisions to test batches manufactured immediately before and after a batch which is found to be out-of-specifications should be provided.

Provisions for withdrawal from the market of any production batch found to be out-of-specifications and, if necessary, those batches immediately before and after the batch in question should be provided.

IV. SPECIFIC CONSIDERATIONS

A. PHARMACEUTICAL DOSAGE FORMS

The section on General Considerations addressed the general aspects for determining the stability of drug components in finished drug preparations. However, it is also appropriate to note that some specific tests are often indicated for certain pharmaceutical dosage forms in addition to those normally conducted. The tests listed below, although not conclusive, should be considered as stability tests of the product.

<u>DOSAGE FORMS</u>	<u>SPECIFIC TESTS INDICATED</u>
Tablets	Hardness measurements Disintegration rate Dissolution rates, where appropriate
Capsules	Dissolution rates, where appropriate
a. Soft-gelatin	Inspection for leaks
b. Hard-gelatin	Visual Examination for brittleness
Suspensions	Viscosity, where appropriate Resuspendability Effects of freezing pH
Ointments, creams, gels and pastes	Homogeneity Viscosity, where appropriate Effects of freezing
Oral Powders	Completeness of solution/or dispersion
Powders for injections	Completeness of solution/or dispersion
Implants	Hardness Dissolution rate Friability
Injections	Sterility Syringeability, where appropriate Effects of freezing Multiple insertions/withdrawals

	pH Testing inverted containers
Solutions	Sterility, where appropriate Effects of freezing pH
Aerosols	Delivered dose Particle size distribution Valve corrosion Spray pattern

B. STERILE PREPARATIONS

Sterility is to be considered as part of the stability profile (shelf-life) of a drug preparation stated to be sterile. Because of storage requirements and the number of samples necessary for sterility testing, the frequency of testing for stability studies should be on the initial date and at the proposed expiration date. The test for sterility that is conducted at the release of a lot is to be considered as the initial date test. If the proposed expiration date is extended, sufficient samples should be anticipated for retention to provide for tests at the extended date.

If methods other than USP are used to test sterility, their adequacy should be demonstrated. The method should be properly referenced. The specific UPS method should be delineated. Non-USP methods should be described in detail.

Ophthalmic Preparations

Sterility is to be demonstrated for all ophthalmic preparations. Specific details for ophthalmic preparations are given in 21 CFR 200.50.

Ampules

Sterility is to be demonstrated on sealed ampules only on the date of manufacture. Since the type of containers is hermetically sealed, this type of seal prevents microbial contamination. The product will be opened only once and used.

Sterile Preparations with Microbial Inhibitors

Sterile preparations whose formulations include added substances (used to prevent microbial growth) to maintain a sterile environment during the product's shelf-life are to be tested for sterility and for levels of the added substances on the initial date of manufacture. After the initial analysis, only levels of inhibitors need be tested for during the regular testing schedules. If a lack of or low levels are found, tests for sterility must be initiated and continued as per the suggested schedule until the expiration date.

Multiple Dose Containers

Those products that are to be marketed in multi-dose containers require special testing to assure that sterility and potency are maintained. In order to properly conduct the test for multiple entry, the container stopper must be entered with a needle and withdrawn the maximum number of times the dosage on the label states. Under these conditions, sterility and potency must be maintained. The bottle contents should be checked for visual stopper particles. The latter may occur upon penetration of the needle into the stopper. Although, the ideal test period should be over the life of the proposed expiration period, the penetration study need only be conducted once and prior to the start of stability studies.

C. TYPE A, B, AND C MEDICATED PRODUCTS

This section provides information for conducting stability studies for medicated feed products, premixes and complete feeds. This section applies only to dry feed products. Liquid feed products and blocks are covered under separate sections elsewhere in the guidelines.

Under the Second Generation regulation published March 3, 1986, two new concepts in the area of medicated feeds were presented. The new concepts consisted of the renaming of feed products in general and adding the requirement of an expiration date.

Under this regulation, the following classifications were provided:

- Medicated premixes are now called **Type A Medicated Articles**.
- Medicated finished feeds are now divided into two (2) different types, viz.,-
 - Type B Medicated Feeds (Supplements, Intermediates, etc.) which must be diluted with feed material or can be fed top-dressed prior to feeding.
 - Type C Medicated Feeds (Complete feeds, blocks, free-choice, etc). (which can be fed "as is" without the need of further dilution)

NOTE: In this guideline, the terms "premixes" and "medicated feeds" and their corresponding types will be used.

1. Expiration Dating Requirements
(Reference: 21 CFR 514.1(b)(5)(x))

a. Type A Medicated Articles (Medicated Premixes)

Expiration date periods are required for all Type A Medicated articles (Premixes). (cGMP: 21 CFR 226.58)

b. Type B Medicated Feed Products

The need for an expiration date for Type B medicated feeds will be evaluated on a case-by-case basis.

c. Type C Medicated Feed Products

The need for or absence of an expiration date for Type C medicated feeds will need to be justified with stability data.

2. Study Temperature and Length

a. Room Temperature

i. Type A Medicated Articles (Premixes)

All medicated premixes should be subjected to a room temperature study. The test schedule will be dependent on the proposed expiration date. Section "Table of Suggested Test Schedule" for Test Schedule.

ii. Type B Medicate Feed Products

Type B products, if prepared and sold as intermediate premixes, should follow the guides for a Type A Medicated (Premix) Articles.

Those Type B products used as Type C products should follow the guides for Type C Medicated Product.

iii. Type C Medicated Products (Complete feeds)

Stability studies for Type C products should be carried out at ambient temperature and RH for a least 90 days. All existing weather conditions must be recorded. (See Section F.2.(v) for definition of ambient temperatures. If temperatures other than ambient are used, then they should be specified.

Test schedule: 0 (initial) 1, 2, 3 months

b. Elevated Temperatures

i. Type A Medicated Articles (Premixes)

All medicated premixes (Type A Medicated Articles) should be studied at an elevated temperature station, (usually 37°C) to at least 6 months.

Test schedule: 0 (initial), 2, 4, 6 months

ii. Type B Medicated Feed Products

Type B products, if prepared and sold as intermediate premixes, should follow the guides for a Type A Medicated Article.

Those Type B product used as Type C products should follow the guides for Type C Medicated Products.

iii. Type C Medicated Feed Products (complete feeds)

When Type C medicated products are studied at elevated temperatures, the study need not be carried beyond a one (1) month period, since feed products at elevated temperatures are likely to become moldy and, therefore, unusable.

Test schedule: 0 (initial), 2, 3, 4 weeks

NOTE: Any testing can be carried to a longer period of time if the usage or data dictates or the sponsor wishes. The Center reserves the right to request longer periods of study if the data so indicate.

If the stability data indicate a shorter period is necessary than that listed above or proposed, then the shorter time period will be required on the label. This action is to alert the user that the product will remain stable for the time period designated. Adjustment or removal of an expiration date for those products not required to have one may be accomplished through the submission of additional data requesting and justifying such action.

3. Product Composition

The stability study should include a study of the medicated premix and the medicated feed product consisting of the active drug ingredient (from the medicated premix) and typical non-medicated feed components. This latter may contain vitamins, minerals, etc. A commercially available feed may be used. The exact formula for the premix and complete feed should be available for the study.

If the exact formula cannot be obtained, the bag or label attached to the bag or available with the bulk product may be submitted.

4. Lots for Stability Study

In order to produce meaningful results, samples from at least 3 production size lots should be tested. Data obtained from pilot size lots will provide only "Tentative" information on which to make an expiration/stability decision.

5. Testing Levels

a. Premixes (Type A Medicated Articles)

The active drug ingredient(s) present must be tested at the labeled level(s).

b. Feeds (Type B and/or C Medicated Products)

Complete feed products must be tested at the appropriate use level or levels of the active ingredient(s) listed on the label.

c. Multiple Drug Ingredients

Where multiple drugs ingredients are proposed for use, the highest and lowest use levels for each proposed ingredient must be tested. Depending on the number of active ingredients in the feeds and recommended use ranges (levels), tests must be conducted at the high-low, low-low and low-high levels.

6. Pelleted Products

The results of analysis of the mash product from with the pellets are prepared must be submitted along with the data/information from pelleted products.

A description of the pelleting conditions should be submitted. Pressures and temperatures at the beginning and end of the pelleting process should be reported. The type of equipment should also be listed.

Analyses of samples should be performed before and after pelleting to obtain an indication of what effect the pelleting has on concentration (potency) and the physical product. The assay schedule should be provided.

7. Moisture Content

Moisture determinations, where necessary, should be made at the time of individual analyses and submitted with assay results. Corrections in calculations should be applied where necessary.

8. Test Results

The following types of information, as a minimum, should be provided for each testing station:

- a. Moisture content, if necessary.
- b. Assay results (adjusted for moisture, if necessary).

NOTE: The initial assay results must always be reported. This is the starting point for all studies.

- c. Any other information relative to the stability study or product.
- d. All raw data including representative spectra or chromatogram of sample and standards related to the method.

NOTE: Assay limits should be determined based on recovery data using sufficient numbers of spiked and actual samples.

9. Additional Studies

The following one-time studies should also be conducted on samples of medicated premixes and feeds:

- a. Interference studies - Combination of Drugs

When two or more active drug ingredients are present these studies are necessary to determine if any interference occurs that will hinder the proper assay of either ingredient. These studies should also be conducted when it is known that similar drug products approved for use in the species under proposal will be encountered in marketing and/or use.

- b. Segregation studies

Where necessary for bulk or bagged materials, analysis of top, middle and bottom samples should be conducted. These studies should be conducted to assure the drug component does not concentrate in one portion of the product or container. The sample

should be transported at least 50 miles (round trip) to simulate actual conditions.

c. Homogeneity studies

Homogeneity studies should be performed on all proposed premix and finished feed products.

For these studies, analysis of top, middle and bottom of bagged or stored bulk samples should be conducted. Bags should be stored in position most commonly used in commercial outlets/storage facilities.

When label directions call for very small quantities (e.g. 2.5 oz.) of the premix to be added to unmedicated feed to make a ton, homogeneity is especially important.

10. Pilot vs. Production Samples

Samples from production-size batches should be used for stability studies. These samples provide for approximate actual use conditions. However, if pilot scale samples are used, this fact should be reported. Laboratory scale samples provide for optimum control of all factors. Therefore, it should be kept in mind that changes may be needed in limits once the drug is approved for use and the "real" or "actual" use situations are monitored and evaluated. Such changes may be provided by the applicant or requested by the Agency. The applicant should use real world conditions as much as possible.

D. TYPE B AND C MEDICATED LIQUID FEED SUPPLEMENTS

The approval of a medicated premix for use in formulating liquid feed supplements calls for different types of stability studies than those indicated for use in dry feeds.

The purpose of stability testing a medicated premix in liquid feed supplements (LFS) is twofold:

- to ensure that the drug substance is chemically stable in general in LFS matrices
- to ensure the drug substance is homogeneously distributed or positionally stable (in general) in LFS matrices during on-site storage before and at the time of use.

Drug stability in a LFS may be tested in specifically developed formulations or in formulas containing ingredients typical of those in current use in the liquid feed industry. See Appendix B.

A drug sponsor under a new application should establish the chemical stability of the drug to be used in a liquid feed matrix. The sponsor may establish whether or not the drug is positionally stable in the matrix or how that stability must be maintained by agitation.

Approval of the use of a specific drug (in a medicated premix) in a LFS will be published in a regulation (21 CFR 558) for use in a matrix with specific parameters.

Manufacturers of liquid feed supplements may use the approved premix for a LFS by submitting data for a formula they wish to produce and use. The data may be submitted under a master file. Approval for use of the LFS will be granted by an agency approval letter under a supplement to the sponsor's NADA.

Appendix A provides information relative to current commonly found physical/chemical parameters used in the liquid feed industry.

Appendix B lists common ingredients generally used in liquid feeds under current practices in the liquid feed industry.

Appendixes A and B are for the drug sponsor's use in obtaining approval for use of the drug premix in all liquid feed supplements with no further need for the liquid feed supplement manufacturer to develop data unless the LFS manufacturer wants to claim that the drug is positionally stable in his liquid feed matrix and no agitation is needed.

1. Protocols

Prior to initiation of any studies for testing a premix containing a drug chemical in a LFS, it is strongly suggested a testing protocol requesting the Center's comments be submitted.

2. Stability Test Information

The following information should be provided to study the stability of any medicated liquid feed formulation:

- a. A complete description of the proposed formulations

This description should provide complete information on the composition of the actual formulation(s) to be used including the potency of the drug ingredients, identification of all other ingredients and the approximate ranges of their use levels.

The description should also provide information on the physical and chemical parameters of the formulation and manufacturing conditions. The latter should include, where appropriate, mixing times, temperatures, etc.

NOTE: The LFS sponsor/manufacturer is responsible to assure that and LFS produced falls within the stability parameters of the matrix.

b. Finished Product Specifications

The specifications should describe:

i. The physical characteristics of the formulation

- appearance
- color
- odor

ii. The chemical characteristics of the formulation

- viscosity data, if applicable
- pH data
- other properties or characteristics
- identification of the active ingredient
- quantitative assay of the active ingredient

NOTE: The data should provide maximum/minimum limits (based on data to verify same), where necessary, unless the actual use or stability data warrants the observance of fixed conditions.

c. Analytical Method Information

The method(s) used to determine the specifications for the active ingredient(s) or other chemical characteristics should be provided.

The method(s) should be provided in detail or be properly referenced to a master file, actual NADA, or appropriate journal.

The assay limits proposed or already established for the LFS product and determined to be appropriate (by data) should be provided. Proper validation data should be provided to support the performance of the method and the proposed assay limits.

d. Conditions of Testing

A complete description of the testing conditions involved in the studies should be provided. Containers, temperatures, intervals for stability testing, sampling techniques, and mixing and storage equipment should be reported.

e. Results of Stability Tests

The raw data should be analyzed and reported. Statistical analysis may be required.

3. Types of Stability Testing

a. Chemical Stability

Applicable to all medicated premix products intended for use in a LFS.

The drug ingredient must be stable, that is, it does not degrade in the matrix proposed. If the drug chemical remains stable but fails to show uniform dispersion in the matrix (in either laboratory or field trials), testing will be expected to show that upon mixing or agitation the drug chemical remains stable and uniformly dispersed in the proposed matrix.

If the sponsor of the application recommends agitation in advance of any use, chemical stability testing may only be necessary. Laboratory testing will be required.

b. Positional Stability

Applicable to those medicated premix products in a LFS matrix not requiring agitation.

A proposed LFS formulation will be considered as positionally stable if appropriate laboratory studies demonstrate that the active ingredient(s) remain dispersed throughout (no significant stratification or layering) the LFS after 8 weeks storage without agitation at 30°C and under refrigeration (2° to 8°C). Stability in the same product must be verified by one field study in which there is no agitation.

If stratification occurs, agitation may be needed to disperse the active ingredient.

4. Stability Testing Studies

a. Laboratory Study

The design of the laboratory studies for both chemical and positional stability should include the following factors as standard requirements:

- iii.* Samples from at least 3 pilot batches manufactured under production conditions.
- ii.* An appropriate container for storage of samples. The container should be described.
- iii.* Samples should be stored undisturbed (i.e., unagitated) at the designated storage temperature of 30°C, and under refrigeration (2° to 8°C).
- iv.* Samples should be taken from the top, middle and bottom of the container contents for analysis. Analysis of the container contents should be performed in duplicate at 0, 2, 4, 6 and 8 weeks. The physical condition/appearance of the container contents should be observed and reported at each time of sampling.
- v.* A short freeze-thaw study for period of at least 5 days should be conducted to indicate the effect of freezing, if any, and the subsequent thawing. Samples should be taken from the top, middle and bottom of container contents for analysis at the end of the 5 day cycle. The condition of the sample should be observed and recorded throughout the study.
- vi.* Other stability tests may be added as deemed necessary to better describe the stability parameters and the stability of the product.
- vii.* If agitation is to be used, the equipment, mixing sequence and time intervals should be described.

b. Field Study

The purpose of the field study is to verify the results of the laboratory studies and to demonstrate if any temperature layering effect may take place when using large, outside storage tanks. In any case, the stability of the product must not be adversely affected.

The field study should include the following:

- i.* Use of an actual batch of the formulation

Only one lot need be studied.

iv. Analysis of the storage container contents

1. A one (1) pint sample should be removed when the tank is full, approximately half-full (50% of capacity) and again at 25% and 10% of capacity. In the case of a positionally stable product, samples should be taken from the top 20% of the storage container, if possible. If not, sample from the delivery pipe. In the case of a product being agitated, remove the sample by the delivery pipe. Any sample removed by the delivery pipe should be taken after discarding any material in the delivery pipe.
2. Samples should be analyzed in duplicate.
3. Analytical results should be within the established assay limits for the labeled active ingredient(s).
4. The physical condition/appearance of the product should be observed and reported when sampling is performed.

iii. Length of the study

The length of the study should be commensurate with the anticipated time interval of storage and use, i.e., intervals when supplies of the LFS are to be renewed, generally not less than 2 weeks and not more than 8 weeks.

iv. Reporting of weather conditions

Existing weather conditions (temperature, wind, rain, etc.) should be described when the tank is filled (full) and when samples are taken.

v. Type of mixing equipment

If the drug fails to show positional stability in laboratory studies, storage tanks with mixing equipment should be used. The equipment, mixing sequence and time intervals should be reported.

c. Lick-Tank Operation

If a user plans to use a lick-wheel system to deliver a LF product, the type of stability testing to be conducted should simulate those conditions to be used in field storage and use, including mixing.

5. Recommended Labeling

Information relative to proper use and mixing and equipment, where necessary to maintain stability of the LFS product should be provided so that proper labeling can be attached to the premix container.

If agitation is necessary for the LFS formulation or if the LFS formulations if found to be positionally unstable, appropriate directions are recommended for placement on the premix container label (which is to be used in preparing the LFS) and any LFS labeling.

a. For liquid supplements stored in recirculating tank systems:

"Because the drug product is not positionally stable in this liquid supplement, recirculate immediately prior to use for no less than 10 minutes, moving not less than 1% of the tank contents per minute from the bottom of the tank to the top.

Recirculate daily as directed in this paragraph, even when the supplement is not used."

b. For liquid supplements stored in mechanical, air or other agitation-type tank systems:

"Because the drug product is not positionally stable in this liquid supplement, agitate immediately prior to use for not less than 10 minutes, creating a turbulence at the bottom of the tank that is visible at the top.

Agitate daily as directed in this paragraph, even when the supplement is not used."

c. If the medicate LFS is found to be chemically and positionally stable in both laboratory and field studies, no agitation instructions will be required on the labels for such LFS products.

APPENDIX A

In survey undertaken by AFMA (now the AFIA) in 1980 which covered about 75% of actual production, a set of physical/chemical parameters (listed below) was found that can be used as guidelines for a typical liquid feed supplement.

Parameter	Low	High	Average
pH	3.8	7.5	5
Total Moisture	27	40	35
Mixing Temp., °F	63	96	81
(°C)	(17)	(36)	(27)
Mixing Time, Min.	17	37	27
Time of Days*	10	45	27

*(Manufacture to Consumption)

APPENDIX B

The 1980 survey indicated the ingredients below commonly compose a "liquid supplement matrix."

The ratios of ingredients in the formula matrix as listed below may be adjusted to arrive at a typical formulation with a pH of about 5.0 and moisture of about 35%.

Sample formula for testing drug stability in Liquid Supplements:

Ingredient	Percent (%) In Formula
Molasses	47
Lignin Sulfonate	10
Condensed Molasses Fermentation Solubles	15
Urea, Dry	8
Corn Steep Liquor	3
Ammonium Sulfate	2
Ammonium Polyphosphate	3
Phosphoric Acid	2
Salt	2
Typical Vitamin/Trace Mineral Premix	8
TOTAL	100.0%

NOTE: The appendices should be used as a guide in the development of a liquid feed matrix. Ingredients other than those listed in Appendix B may be used because of availability, convenience, research, new technology or proposed use. Users should be aware that use of such new ingredients may cause a change in parameters listed in Appendix A. In any case, the liquid feed supplement will be evaluated as presented.

E. MEDICATED BLOCKS

Medicated blocks are compressed feed material (which contain medication) that is shaped into a cubic form for animal free-choice use. Medicated blocks are considered as Type C medicated products.

1. Stability Study

The most meaningful stability data will be that obtained on field samples stored under the same conditions as those blocks consumed by cattle. The data can be obtained from samples used during efficacy trials or the development of consumption data. These blocks should be stored so that animals do not disturb them.

The information should include:

- a. The formulation representative of the product to be marketed.
- b. Components and composition of the various formulations on which the study is to be conducted.
- c. Description of procedures used in preparation of the blocks, including temperatures, pressures and other parameters used.
- d. Data developed on blocks stored under warehouse conditions since blocks may be stored for some time before being placed on the range. Under simulated warehouse conditions, samples should be stored at 25°C and 37-40°C for six months.
- e. Data developed on blocks placed on the range for consumption. Actual weather conditions should be provided, e.g., temperature, cloud cover, rain, snow, etc.

Since consumption rates vary, it is not possible to state the length of time that a stability study should be conducted under range conditions. As a general rule, the blocks should be in the field at least for 14 days but not more than 90 days.

- f. The schedule of testing stations.
- g. The method of sampling the blocks for tests. Basically, all samples should be taken from the surface and from a core of the block. However, an applicant may propose a different technique.

- h. A stability-indicating and validated analytical method.

NOTE: Samples of the mash product used to manufacture the block should be retained for analysis. The results of the analysis should be reported with the block results.

2. Label Statement for Usage

A procedure for determining the type of label statement that will provide added assurance that blocks do not remain on the range beyond the period of satisfactory stability is as follows:

- a. The available stability data should be reviewed and the time interval should be determined over which the drug(s) exhibits satisfactory stability.
- b. On the basis of stability data, daily consumption, and size of the block, a label statement should be developed that will indicate how blocks are to be used and when new blocks should be placed for use.
- c. Formula to determine label statement:

$$\text{No. of cattle (per block)} = \frac{A}{B \times C}$$

Where:

A = weight of block (lb)

B = lbs/animal/day

C = number of days

For example:

If the drug has exhibited satisfactory stability for 2 weeks (14 days), the average daily consumption is 1/4 lbs and the block weighs 28 lbs, the label should say, "Use one block for every eight (8) cattle. NEW BLOCKS SHOULD BE PLACED OUT IN APPROXIMATELY FOURTEEN (14) DAYS."

F. SOLUBLE POWDERS AND DRINKING WATER

1. Soluble Powders

Medicated soluble powders for the preparation of drinking water are expected to remain stable for the projected shelf-life of the product.

Samples should be stored both at 25°C and at 37-40°C. In addition, to testing for drug strength, storage samples should also be tested for moisture content, solubility (dissolution of the powder in a solvent), caking, and pH of solution.

Soluble powders are considered pharmaceutical dosage forms and, therefore, must be manufactured according to the cGMPs under 21 CFR 211.

Stability studies should be run on the solution containing the dissolved powder over the labeled storage period. Appropriate restrictions should be stated on the label where necessary.

2. Drinking Water

Medicated drinking water should exhibit adequate stability for the time period(s) indicated on the label.

Medicated drinking water should be prepared using both soft and hard water and stored both at temperatures of 25°C and at 37-40°C in metal troughs, including rusty troughs, for stability testing. For concentrated solutions stored at both temperatures in representative metering devices, the storage period should correspond to the maximum time during which the concentrate remains efficacious and safe.

If ambient temperatures or those other than that stated above for the above studies are used, all existing condition must be described.

Proportioner concentrate assays and use level assays should be provided.

NOTE: In conducting the above tests, local drinking water (whether well or municipal) should be used. It is not necessary to develop "specially" prepared water for testing, since it will not reflect the "real world" use.

G. ORAL DRENCHES

Drenches for oral administration may be available either as powders or as concentrated solutions or suspensions. They may also appear as solutions or suspensions ready for use.

Drenches are considered pharmaceutical dosage forms and must be manufactured according to the cGMPs under 21 CFR 211.

In all cases, the product, at the time of use, should meet the general requirements for chemical stability and maintain, under expected storage conditions, a reasonable degree of physical integrity, such as, absence of caking, sticking, gross discoloration or irreversible loss of suspension or solution of the product.

Maintenance of adequate physical and chemical stability of partially used liquid products is necessary. If this product shows degradation, then a label restriction against reuse may be required.

NOTE: In conducting the above tests, local drinking water (whether well or municipal) should be used. It is not necessary to develop "specially" prepared water for testing, since it will not reflect the "real world" use.

H. MILK REPLACERS

In addition to the data requested in the general guidelines for the stability of the product as a drug dosage form, recovery data should be submitted to show that the drug to be used as a milk replacer is stable in solution for the length of time stated on the label.

Medicated milk replacers should be prepared using both hard and soft water. They should be stored at temperatures of 25°C and 37-40°C in their market containers (metal, synthetic rubber and/or plastic) for the length of time stated on the label. If temperatures other than 25°C are used, e.g., ambient temperature, that temperature plus weather conditions must be described and reported.

Data must also be developed to show that the drug is homogeneously mixed and distributed in the milk replacer solution.

NOTE: In conducting the above tests, local drinking water (whether well or municipal) should be used. It is not necessary to develop "specially" prepared water for testing, since it will not reflect the "real world" use.

I. MASTITIS PREPARATIONS

The stability tests for mastitis preparations are basically the same as for solutions listed under pharmaceutical dosage forms.

Tests for stability should include:

- Appearance
- Potency
- Suspendability

- Syringeability
- Leaching data for syringes
- Freezing
- pH Measurement

J. SUSTAINED – RELEASE PRODUCTS

In addition to the specific stability tests that are required for the particular dosage form, the stability study should include assays for the release pattern of the active ingredient. Because of the nature of these types of drugs, drug release patterns or rates should be measured by dissolution tests. When microencapsulated sustained-release dosage forms are to be studied, measurement of the capsule particle size range distribution, including ratios of core to wall thickness, may be necessary.

K. MICROENCAPSULATED PRODUCTS

Microencapsulated drug products offer specialized drug delivery systems and dosage form characteristics that may prolong the shelf-life of the drug. In addition to the specific stability tests that are recommended for the particular dosage form, the measurements during the course of the stability study should demonstrate that properties claimed for the microencapsulated product have not been diminished or destroyed during storage. Maintenance of the integrity of the wall material should be demonstrated.

L. VAT DIPS

In addition to the specific stability information recommended for the particular marketed dosage form, stability studies of vat dips, i.e., the dosage form dissolved in the recommended solvent system for use should include active ingredient assays and pH. Such tests should be conducted at intervals to the period proposed on the label of field storage.

M. rDNA PRODUCTS

rDNA derived or "genetically engineered" active ingredients will be administered to animals using available conventional delivery systems, e.g., tablets, capsules, solutions, etc. Stability studies for products containing drug chemicals derived from rDNA techniques should be the same as those conducted for the particular dosage form. Other tests related to the manufacture of the product may be necessary and will be determined on a case-by-case basis.

NOTE: rDNA type products are often called "Bio-Tech" products.

N. DRUG SUBSTANCES

Even though the Stability Guidelines are mainly related to finished dosage forms or medicated products (Type A, B or C), the concepts are applicable for performing studies on drug substances or raw materials used in the manufacture of the final dosage form.