

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.

For questions regarding this guidance document, contact Dr. Dennis M. Bensley, Jr., Center for Veterinary Medicine (HFV-140), Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855, (240) 276-8268.

Additional copies of this guidance document may be requested from the Communications Staff, HFV-12, Center for Veterinary Medicine, Food and Drug Administration, 7519 Standish Place, Rockville, MD 20855, and may be viewed on the Internet at <http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry>.

**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. Kenyon, 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

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.