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BUA

DRUG DEVELOPMENT

Blend Uniformity Analysis

'...Applies to all new ANDAs and ANDA Supplements...

IMPACTS ON ANDAs

Guidance to Industry

ANDAs: Blend Uniformity Analysis

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INTRODUCTION

Eighteen months ago (Aug '99) the FDA issued its Guidance to Industry notes on blend Uniformity Analysis with the acronym of BUA. To date Mar. 2001 the guideline status has remained unchanged in its draft form

FDA's Draft BUA GUIDELINE is 10 months old

This **draft** guidance is intended to provide recommendations to applicants of abbreviated new drug applications (ANDAs) on establishing in-process acceptance criteria for blend uniformity analysis (BUA).

This **draft** guidance provides recommendations on when BUA should be performed and how to perform BUA. The recommendations apply to original ANDAs and supplemental ANDAs for formulation and process changes.

BUA Analysis Applies to ANDAs & Supplements

FDA's regulations state that the information submitted to support applications must include in-process controls for the drug products (21 CFR 314.50(d)(1)(ii)(a) and 314.94(a)(9)(i)).

The Center for Drug Evaluation and Research (CDER) guidance for industry on *Submitting Documentation for the Manufacture of and Controls for Drug Products* (February 1987) is currently being rewritten and states that:

"The analytical controls used during the various stages of manufacturing and processing of the dosage form should be fully described.

Where feasible, the in-process specifications should be supported by appropriate data that can include, but should not be limited to, representative master/batch production and control records."

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FDA is currently rewriting its 1987 Guideline:-

"Submitting Documentation for the Manufacture of and Controls for Drug Products"

BUA is an in-process test that is useful for ensuring the adequacy of the mixing of active pharmaceutical ingredients (APIs) with other components of the drug product.

The in-process testing requirement for adequacy of mixing to ensure uniformity and homogeneity is established at 21 CFR 211.110(a)(3).

Recommendations are provided in this guidance on the following:

- BUA testing for certain dosages, based on their composition, according to strength
- (mg of active) and weight to weight percent (w/w% of the active)
- Sample size and procedures
- Acceptance criteria for blend uniformity analysis

FDA intends to seek the support of the Product Quality Research Institute on blend uniformity.

BUA & the USP's Content Uniformity are linked together

This guidance will be updated based on the outcome of any research.

II. SCOPE

BUA is recommended for those drug products for which the U.S. Pharmacopoeia (USP) requires content uniformity analysis.

USP requires this test when the drug product contains less than 50 milligrams of the active ingredient per dosage form unit, or when the active ingredient is less than 50 percent of the dosage form unit by weight.

Products requiring BUA Testing

IR Tablets
MR Tablets
Hard gelatin Capsules IR
Hard gelatin Capsules ER / SR
SGC filled with pastes or suspensions
MDI (IR/ER/SR)
Transdermal Products
Suppositories

BUA is recommended for bioequivalence lot testing and commercial production batches of a drug product. [validation lots]

BUA or homogeneity testing can be applied to all dosage forms, but is recommended for those dosage forms for which the USP requires content uniformity testing. Ref. USP 24, <905>, Uniformity of Dosage Units.]

These dosage forms include:

- Coated tablets, other than film coated tablets
- Transdermal systems
- Suspensions in single-unit containers or in soft capsules
- Pressurized metered-dose inhalers
- Suppositories

If the composition of the drug product is greater than or equal to 50 milligrams of the active ingredient per dosage form unit or the active ingredient is greater than or equal to 50 percent of the dosage form unit by weight, blend uniformity analysis is not usually necessary (see Table 1).

For complex dosage forms, such as modified-release tablets or capsules, and complex processes (e.g., multistep granulation processes), applicants are advised to consult the appropriate chemistry reviewing division to determine if BUA is recommended (see Table 2).

When to Test for BUA

Development Stage
Process Qualification Lot
Regulatory Stage
The Pivotal / Bioequivalence Lot
Commercial Stage
Three validation Lots
Each production lot

Under current good manufacturing practices (CGMPs), an applicant is required to perform a test or examination on each commercial batch of all products to monitor the output and validate the performance of processes that could be responsible for causing variability, which includes adequacy of mixing to ensure uniformity and homogeneity (21 CFR 211.110(a)(3)).

Up to 10X sample weight is acceptable when scientifically justified in ANDA

A BUA test for commercial batches in an approved application meets this requirement.

An applicant should not submit a supplemental application requesting the deletion of BUA testing from commercial batches when the BUA test is also used to ensure compliance with CGMPs.

A supplement requesting deletion of BUA testing should include supportive information justifying that the test would not be considered necessary under cGMPs.

Requests for deletion of BUA testing as an approved in-process specification do not relieve a firm of its responsibilities for compliance with CGMPs.

Where an approved application does not include a BUA for commercial batches, conformance with the CGMP requirement will be evaluated under the drug CGMP regulatory program.

SAMPLING SIZE AND PROCEDURES

The recommended sample size of the blend material is no more than **three times** the weight of an individual dose. If the firm experiences problems in collecting small samples equivalent to 1 to 3 dosage units and demonstrates that small samples give lower values for BUA due to sampling bias, larger samples (usually no more than **10** dosage units) can be collected.

Justification for larger samples should be specific to the application under review.

Using the three times sampling rule is statistically best

Justification based on literature references is usually not adequate. Samples for BUA can be collected either from the drums or the blenders.

For more than one drum or blender, analysis from each drum or blender is encouraged for the bioequivalence and / or test batches.

Collect samples from final blender as (both arms) multi-drum sampling increases analysis

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The batch size, number of samples (usually 6 to 10), locations of sampling, and equipment should be specified as part of the in-process controls for BUA or homogeneity.

Potential differences in mixing efficiency associated with specific types of equipment should be considered when determining sampling locations.

BUA is recommended for all active ingredients present in the drug product. Since the purpose of BUA is to assess the uniformity and homogeneity of a blend, composite sampling from various sites is not appropriate.

The weight of the sample tested should be equivalent to the dosage used.

To Composite BUA samples is a GMP violation

If a common blend is used for the manufacture of multiple strengths of the drug product, the weight of the sample used should be equivalent to the weight of the lowest strength of the drug product.

For a drug product where different strengths are not made from the same common blend, BUA for each blend is recommended.

Take a three times sample of the lowest strength weight

ACCEPTANCE CRITERIA AND ANALYTICAL PROCEDURES

Manufacturing records for bioequivalence batches, test batches, and commercial production batches for drug products for which BUA is recommended should include documentation of test results and acceptance criteria for BUA.

Sample the lowest strength weight for BUA

Analytical procedures for BUA can be described separately in the section of the ANDA application (Section XII) on in-process controls. Refer to the FDA guidance for industry on *Organization of an ANDA* (February 1999).

Acceptance criteria of 90.0 percent to 110.0 percent of the expected quantity of active ingredient (mean of individual test results) with a relative standard deviation (RSD) of no more than 5.0 percent are recommended for BUA.

Analytical RSD's on BUA Assays NMT 5.0%

This will allow compensation for any potential loss in blend uniformity during subsequent manufacturing steps and also ensure compliance with USP acceptance criteria for content uniformity.

The BUA results should be reported as individual test results, mean value, and calculated RSD.

Round up to the first decimal place only (i.e. 99.8%)

Rounding of BUA results to whole numbers is not recommended. Additional levels of testing through the use of two-tier acceptance criteria are also not recommended.

BUA results may change after compression/filling

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About this DRAFT Guideline

WHO Prepares

This guidance has been prepared under the direction of the Chemistry, Manufacturing, and Controls [1] Coordinating Committee (CMC CC) in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

FDA's Best Thinking

This guidance represents the Agency's current thinking on blend uniformity analysis for ANDAs. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes, regulations, or both.

Tablets & Capsules

The primary application of this guidance is expected to be in the manufacture of solid oral dosage forms, although certain other dosage forms are covered by the document.

To simplify the document, blend uniformity analysis has been discussed in this guidance in the context of solid oral dosage products.

The principles discussed in this guidance apply equally to other types of blends and dosage forms.

New FDA Rewrite

An earlier guidance entitled *Submitting Documentation for the Manufacture of and Controls for Drug Products* (February 1987) is currently being revised. When that document is finalized, the contents of this guidance will eventually be incorporated and extended, as appropriate, to new drug applications (NDAs).

FDA'S COMMENTS – May 2000

Q. - ***Does*** the OGD Draft Guidance document on **Blend Uniformity Analysis** (BUA) represent current GMP requirements?

References: Draft Guidance for Industry ANDAs: Blend Uniformity Analysis August 1999 21 CFR 211.110 Sampling and testing of in-process materials and drug products.

A. - **NO** the Office of Generic Drugs (OGD) guidance document currently presents recommendations for application filing based on 21 CFR 314, not on cGMP regulations. Also, this is a **draft** document subject to review and comment, and has not yet been implemented (as of May 2000).

FDA's
Blend Uniformity Analysis
is still in a draft stage
It is not cGMP or
CFR 21

OGD current policies are based on earlier policy documents rather than on this draft guidance. Additionally, the guidance document presents recommendations only, not requirements.

Alternative approaches may also be used to submit data with an application.

Three times the
tablet/capsule weight
is the correct
statistical number

Note:
"A one unit dose sampling (x1) is simply a snap shot of the bulk dry mixed material

The CGMP regulations, 21 CFR 211.110, do not require Blend Uniformity Analysis (BUA).

It requires some type of test or examination on each batch, but that test or examination does not have to be BUA as described in the guidance document.

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Generally Tapped & Bulk Density & particle size Are the best granule conformity controls

Failure to perform BUA type testing on online production batches should not be cited as a CGMP deficiency.
BUA type testing is recommended for low dose powder blend products (e.g., less than 50% or 50 mg) but other approaches may also be used to satisfy this CGMP requirement.

For Low Dose Units Tapped & Bulk Density + Content Uniformity using 3 times unit weight is adequate testing

The draft guidance also permits the submission of a supplement to delete BUA testing. This is also an application filing issue and does not exempt a manufacturer from the CGMP requirement for some type of test or examination on each batch.

If BUA type testing is discontinued, an alternate approach to comply with 21 CFR 211.110 should be implemented.

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Essential Reference for R&D & RA for all pharmaceutical firms

Title Page Image - with courtesy of the original FDA CDER web site at www.cder.fda.gov/

Table 1.

Blend Uniformity Analysis Recommendations for Simple Dosage Forms

Weight of Active Pharmaceutical Ingredient(s) Per Dosage Form Unit				
0 mg →		50mg →		+++mg
	Blend Uniformity Analysis recommended		Blend Uniformity Analysis not usually needed	
0%		50%		100%
Active Pharmaceuticals Ingredient(s) as a Percentage of Dosage Form Unit by Weight →				

Table 2.

Blend Uniformity Analysis Recommendations for Complex Dosage Forms and Complex Processes

Complex Dosage Forms are:				
◆ Modified-Release Tablets ◆ ER/SR Capsules ◆ ◆ Complex manufacturing Processes involving multistep granulation processes				
Weight of Active Pharmaceutical Ingredient(s) Per Dosage Form Unit				
0 mg →		50mg		+++mg
	Consult Division of Chemistry I or II, Office of Generic Drugs for Guidance Regarding Blend Uniformity Analysis			
0%		50%		100%
Active Pharmaceuticals Ingredient(s) as a Percentage of Dosage Form Unit by Weight →				

Development SOPs

'…the essential internal standard system of a successful drug development unit…'

Standard Operating Procedures (SOPs) for drug development applies to individuals or groups responsible for the management and operation of the innovative/generic drug development unit. It is equally valuable for the operation and control of the CMC (chemistry, manufacturing and control) section of a NDA researched-based unit.

All pharmaceutical companies conducting drug research and development *must* have understandable SOPs. The primary purpose of the SOP is to translate the various regulations and guidelines, which are open to interpretation, into clear and concise sets of instructions.

Don't Do Without Development SOPs

Essentially generic development can be distilled into standard development procedures which any development scientist could apply.

These procedures may be electronically circulated as a read-only documents. Master copies authorized and stored by QA using the new electronic signature procedure (e-sig rule of 20 October 1997).

Distribute e-SOPs electronically

A researcher conducts work according to a documented set of procedures - which hopefully represents the best and most current methods available i.e. drug development via "state-of-the-art" techniques.

A drug researcher must keeps a record of every detail of the product development - both the advances *and* the failures of the experimental batch lots. SOPs also demonstrate that you are following a key rule of a good researcher - that the research procedures are fully described so that they can be replicated where necessary.

Remote-US Drug Development.

The Standard Operation Procedures that govern Non-US drug development of the innovative/generic dosage form must be carefully structured to insure that the development procedures are fully understood and interfaced with the US manufacturing facility.

Manufacturing equipment and scale-up procedures require dove-tailing at both facilities. Analytical and microbial laboratory test methods need to be rugged and operational in both facilities.

Great care needs to be taken to insure and demonstrate the robustness of these laboratory tests and analyses.

Testing procedure methods should be chosen in close cooperation with the production laboratory facilities to insure a smooth transfer of technical documentation (TTD requirements).

The Standard Operation Procedures chosen, must fully represent a cross-section of the SOPs needed for a drug development unit to operate efficiently and to produce drug products *on time*.

The SOP index in this journal supplies all the major procedures required, while the summary SOPs chosen describe the purpose and the principles generally needed to meet the scientific, regulatory and at times GMP objectives of a well run stability unit.

Carefully written SOPs will save research based firms and generic developers time and hard pressed development dollars.

Standard Operation Procedures

The SOP index of about three hundred development SOPs provides the reader with a full overview of the written SOP requirements for functional drug development departments, namely pharmaceutical, analytical, microbiological and lastly the key stability unit.

Regulatory Audit SOPs are an Essential Pre-submission Requirement

Regulatory SOPs are a specialized area and should cover all regulatory aspects of Drug Development. Pre-submission file review and presentation of the Product Annual Report are two key examples of Regulatory SOPs.

Generic Development of pharmaceutical drugs may take place in a Non-US development laboratory facility. Where product development occurs in a remote development unit (i.e. not attached to the proposed manufacturing site - special SOPs dovetailing the procedures at the remote and manufacturing site are necessary for such a separated situation.

Emphasis has been placed in certain SOPs on external development (outside the US) while commercial manufacturing *is* targeted at a US commercial site. In the majority of the SOP examples the regulatory 'Pivotal' batch for regulatory inclusion into the NDA/ANDA submission file, is targeted for manufacture at the US commercial manufacturing site.

Oversees developers who have FDA inspected / approved commercial manufacturing facilities may produce the pivotal batch at a non-US small or large scale manufacturing facility. The manufacturing and testing facility must be in full GMP compliance, as if it *were* a US based operation.

Non-GMP R&D or drug development facilities are *not* suitable for clinical or *pivotal* drug manufacturing. Full cGMP *pilot plants* or to use the more appropriate terminology 'small scale manufacturing' facilities are the correct venue for manufacturing clinical batches.

Although this procedure may be within the OGD framework of regulations, it is not a recommended route, if the object is to routinely manufacture at an approved US commercial production site.

Pivotal batches for regulatory submission to the authorities should always be manufactured at the US commercial site - if the intended generic market is the USA.[3]

Stability SOP Development

'...operating a functional stability unit...

This section summarizes the Stability Units' foremost Standard Operating Procedures (SOPs).

Handling SOPs in an ordered manner may well be the solution to the effective development of a generic or innovative drug development program, not only to place the newly formulated drug product on the fast track to approval but hopefully to save embarrassing moments during a pre-approval inspection (PAI) should the agency investigator stumble onto failing drug product stability results in a product-specific PAI review.

Key Standard Operating Procedures are summarized to highlight the myriad of procedures required for the correct handling of stability results *and* stability failures in an ongoing drug stability study, - be it a developmental or a final formula i.e. a finished product *ready to go* for submission.

How does your firm shape up in this stability line-up? If you don't have the Stability SOP in place, - what is the firm doing about it? How is the stability department handling the specific stability requirements? Have all stability programs and protocols involving the following subject matters been thoroughly aired and discussed in your firms stability unit ?

Handling the standard procedures correctly may well establish the validity or non-validity of the firms stability programs and the actual stability results obtained.

The following SOP summaries, represent a minimum number of essential stability study SOPs required to maintain an operational stability department for either a generic or innovative (researched-based) drug development program and in full GMP compliance for the stability testing of developmental, regulatory and once a year commercial production batch lots.

4

S-005-02-01YY Indexing procedure for Stability Studies.

The purpose of this standard operating procedure is to establish an index and an annual supplementary index for stability study SOPs. The supplementary index allows for new SOPs, or updated existing SOPs, to be indexed in the supplement and distributed in *real time*.

4

S-010-02-01YY Index for Stability Studies.

The purpose of this standard operating procedure is to index the Stability SOPs as shown above. **4**

S-015-02-01YY Initiating a Stability Study.

The purpose of this standard operating procedure is to define the stages and documentation required in order to *start or initiate* a development, pivotal, or commercial stability study.

4

S-020-02-01YY Contents of a Stability Protocol.

The purpose of this standard operating procedure is to define the parameters needed in the stability protocol that meet the specific FDA regulatory requirements.

4

S-025-02-01YY Setting limits for check specifications in a Stability Study.

The purpose of this standard operating procedure is to establish the development procedures for setting upper and lower specification limits for the release and stability (check) specifications for a Stability Study.

4

S-030-02-01YY Number and size of batches for stability testing.

The purpose of this standard operating procedure is to establish the procedure for determining the number and sizes of batches commonly required from development to commercial batch, stability study purposes.

4

S-035-02-01YY Number of samples required for performing stability tests.

The purpose of this standard operating procedure is to establish the number of samples required for performing the analytical tests in a Stability Study. This SOP is specific for each dosage form under evaluation.

4

S-040-02-01YY Storage configuration of samples in a stability environment.

The purpose of this standard operating procedure is to determine the storage configuration of the stability samples in the climatic controlled rooms or chambers during the course of the stability study.

4

S-045-02-01YY Stress testing the bulk drug substance for stability analysis.

The purpose of this standard operating procedure is to determine the stress testing procedures and parameters for an approved supplier of the active drug substance. The data is used for impurity evaluation and method validation.

4

S-050-02-01YY Intervals and climatic and storage conditions for a US development Stability Study.

The purpose of this standard operating procedure is to define the intervals and storage conditions for conducting *formulation* stability studies intended for ANDA/OTC formulations for US approval in accordance with the FDA-EU-Japan ICH Guidelines.

4

S-055-02-01YY Intervals and climatic conditions for a US Pivotal /Bioequivalence Stability Study.

The purpose of this standard operating procedure is to define the intervals and storage conditions for conducting, *Pivotal* and commercial stability studies intended for ANDA and OTC formulations for US approval in accordance with the FDA-EU-Japan ICH Guidelines.

4

S-060-02-01YY - Intervals and climatic conditions for a US validation/PM Stability Study.

The purpose of this standard operating procedure is to define the intervals and storage conditions for conducting *Validation and Post Marketing* stability studies intended for ANDA / OTC formulations for US approval.

4

S-065-02-01YY - Placing the Reference Listed Drug (RLB) on Stability.

The purpose of this standard operating procedure is to establish the procedure for placing batch lots of the reference listed drug on stability in order to evaluate the RLD's analytical parameters, aging and impurity profile at different time intervals and different RLB manufacturing dates in order to produce an overview of the reference drugs stability parameters (e.g. especially dissolution and impurities) (produces a set of mean curves over a year).

4

S-070-02-01YY - Determining the 'Due dates' for a Stability Study protocol.

The purpose of this standard operating procedure is to determine the *'due dates'* (individual testing stations) at which samples are taken from the controlled storage environment for the purpose of analytical testing according to the stability protocol.

4

S-075-02-01YY - Setting the 'Start date' for a Stability Study.

The purpose of this standard operating procedure is to determine the 'start dates' at which samples are placed in controlled climatic condition according to the stability protocol. This procedure determines the time limitations between each step in the procedure.

4

S-080-02-01YY - The initial Certificate of Analysis at T^o for a Stability Study.

The purpose of this standard operating procedure is to initiate appropriate time frames for starting a Stability Study not later than 30 days (according to current guidelines), after the sample has been fully QC tested and a *regulatory valid* certificate of analysis (C-of-A at time zero (T^o)) has been issued. Where samples exceed this period new C-of-A are issued

4

S-085-02-01YY - Packaging procedures on Formulation lots for a stability study.

The purpose of this standard operating procedure is to determine the packaging procedures and quality control functions on development formulation lots for a Stability Study. The number of units packed and the sampling protocol is clearly established.

4

S-090-02-01YY - Packaging procedures on the Process Qualification Batch for a stability study.

The purpose of this standard operating procedure is to determine the packaging procedures and quality control functions on the final process qualification lots for a Stability Study. The number of units packed and the sample protocol is clearly established.

4

S-095-02-01YY - Representative sampling procedures during batch packaging of stability samples.

The purpose of this standard operating procedure is to define the sampling protocol used during packaging procedures in order to accomplish a

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fully representative sampling operation of the entire batch.

4

S-100-02-01YY - Container-Liner-Closure systems for a Stability Study.

The purpose of this standard operating procedure is to specify the container-closure-liner parameters required for product testing from product development to the process qualification stage and the final validation/commercial lots.

4

S-105-02-01YY - Certification of a Container -Liner-Closure system.

The purpose of this standard operating procedure is to establish the vendor and in-house documentation requirements in order to meet the FDA documentation filing requirements for container-liner-closure systems. The contents of each document is briefly described.

4

S-000-02-01YY Labeling of Stability Study Samples.

The purpose of this standard operating procedure is to specify the procedure and exact label data requirements for labeling stability study samples.

4

S-115-02-01YY Storing the stability study samples under controlled conditions prior to analysis.

The purpose of this standard operating procedure is to establish the storage conditions under which stability samples are kept during the interim period between the sample “due date” and the time prior to laboratory analysis to prevent sample spoilage.

4

S-120-02-01YY Reporting test results of a Stability Study.

The purpose of this standard operating procedure is to determine the procedure for reporting and recording of the stability test results at each test interval in the analytical laboratory. The procedure for averaging, reviewing and distributing the test results are documented.

4

S-125-02-01YY Procedures for handling abnormal or OOS results in a Stability Study.

The purpose of this standard operating procedure is to establish the procedure for investigation into abnormal assay fluctuations or out-of-specification (OOS) results in the analytical and microbiological stability program testing.

4

S-130-02-01YY The control of Analytical methods #’s and Edition #’s in stability documentation.

The purpose of this standard operating procedure is to ensure that the correct analytical *methods* numbers and *edition* numbers are used in the analytical and microbiological testing laboratory, and are specified in the stability documentation during the course of a Stability Study. This SOP insures that method changes are updated in the stability documentation.

4

S-135-02-01YY Cross-referencing laboratory notebooks with computerized stability documentation.

The purpose of this standard operating procedure is to cross-reference laboratory analytical and microbiological notebooks containing the raw data at each specific test interval with the computerized stability documentation.

4

S-145-02-01YY Auditing stability data in laboratory notebooks.

The purpose of this standard operating procedure is to determine the method of auditing the stability testing raw data in the laboratory notebooks (analytical and microbiological) and to ensure the precise computerization of the stability data reports.

4

S-150-02-01YY Recording stability study climatic conditions

The purpose of this standard operating procedure is to ensure the correct recording procedures, of temperature and humidity control charts for the climatic chambers or controlled environment rooms. Breakdown procedures of chart recorders and corrective action are documented.

4

S-155-02-01YY Review and control of temperature and humidity recording charts.

The purpose of this standard operating procedure is to ensure the correct review, audit and record keeping of temperature and humidity control charts for a climatic chambers or controlled environment rooms.

4

S-160-02-01YY Periodic revalidation of climatic rooms and chambers.

The purpose of this standard operating procedure is to ensure the periodic revalidation of the climatic rooms and chambers to secure that the temperature and humidity is within limits at all points where samples are stored in the controlled area.

4

S-170-02-01YY Sanitation and house-keeping requirements of climatic chambers.

The purpose of this standard operating procedure is to specify appropriate sanitation and house-keeping practices, conditions and requirements of climatic chambers and controlled environment rooms.

4

S-175-02-01YY Fault correcting procedures (after breakdowns) during a Stability Study.

The purpose of this standard operating procedure is to determine the procedures to follow after a breakdown or failure of the equipment or power supply during an ongoing stability study. The use of hand thermometers and recording logbooks and the corrective action procedure is documented.

4

S-180-02-01YY - Emergency procedures during a Stability Study.

The purpose of this standard operating procedure is to is to determine the procedures to follow after a *permanent* breakdown or failure of the climatic chambers equipment (motor burnout/probe failure) during an ongoing stability study. Corrective action procedures are documented.

4

S-185-02-01YY Reserved.

The purpose of this standard operating procedure is to identify specific in-house SOPs due to unique conditions, methods or equipment operating within the companies development operational procedure.

4

S-190-02-01YY Conditions for stopping a Stability Study.

The purpose of this standard operating procedure is to define the precise conditions subject to which an ongoing stability study will be terminated.

4

S-200-02-01YY - The layout and format of a Regulatory Stability Report

(i.e. the filed FDA report)

The purpose of this standard operating procedure is to define the contents and data fields as well as the document layout and format of a regulatory stability report ready for filing with an FDA agency.

4

S-210-02-01YY- Self inspection procedures in a stability department.

The purpose of this standard operating procedure is to provide for self inspection procedures according to the written in-house compliance program specific for the stability department.

4

S-220-02-01YY - Using stability SOPs and compliance program as stability training tools.

The purpose of this standard operating procedure is to highlight the training tools established in order that appropriate training procedures are provided to the departmental personnel with specific respect to standard operating procedures and in-house compliance programs.

4

S-225-02-01YY - The Do's and Don'ts of a Stability Study - a departmental training tool.

The purpose of this standard operating procedure is to document a check list for departmental training purposes of common practice to follow and to avoid when performing stability studies.

4

S-230-02-01YY - Stability department compliance staff training

The purpose of this standard operating procedure is to provide a written Compliance and stability procedure, detailing specific training programs and frequency for the stability department personnel.

4

S-235-02-01YY - Documentation requirements for a Stability Study - contents of a Stability Dossier

The purpose of this standard operating procedure is to provide a check list and explanation of all the documentation and data forms required to make up the complete contents of a Stability Study Dossier.

4

S-240-02-01YY - Job description of stability department personnel

The purpose of this standard operating procedure is to document and provide appropriate job descriptions (and a training outline) for the personnel in the stability department or personnel involved in the performance of stability related functions.

4

S-245-02-01YY - Review and auditing stability study documentation.

The purpose of this standard operating procedure is to review and audit and review each stability study performed in order to ensure that all documentation from laboratory Notebooks to computerized stability reports are accurate and complete.

4

S-250-02-01YY- Accepting and Signing-off a Completed Stability Study.

The purpose of this standard operating procedure is to specify the acceptance and signing-off procedure by the Quality Assurance Unit for a completed stability study to ensure that the study is in fact complete.

4

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DO'S AND DON'TS OF A STABILITY STUDY
A DEPARTMENT TRAINING TOOL.

1. PURPOSE

The purpose of this **S**tandard **O**perating **P**rocedure is to document an audit check list for departmental training purposes of common practice to follow and pitfalls to avoid when performing stability studies.

2. RESPONSIBILITY

ˆ Symbol indicates work is performed by Stability Manager.
‰ Symbol indicates work is performed by Stability Technicians.

3. FREQUENCY

Performed in the stability department.

4. PROCEDURE

In setting-up a stability unit it is necessary to highlight common deficiencies found in Pharmaceutical Stability Departments, as well as indicating the necessary control structures required for the efficient operation of a functional Stability Department.
The structure of a practical and operational proven stability department is emphasized with:

- correctly formatted Stability Reports (for agency review chemists).
- adequate environmental control on temperature and humidity (review of recording graphs) - reviewed by PAI site inspectors.
- skillfully written SOPs - for efficient daily operation (reviewed during PAI site visits).

Do & Don'ts to follow in your training program:-

Do - insure that Stability SOPs are regularly updated annually or bi-annually.

Do - insure the instructions and details in the SOPs are adequate and sufficient to assure consistent and repeated operation by staff, reading the SOPs.

Do - train and re-train staff in the correct use and understanding of current SOPs.
(Avoid stability and quality control laboratory personnel displaying a non-awareness of the departmental SOPs in their essential day-to-day work).

Do - provide frequent departmental training in 'reviewing and under-standing' the principles of the SOPs.

Do - check the firms SOPs adequately cover all aspects of stability operations required by the FDA or Agency.

Do - check staff are aware of latest *edition* of the Stability SOPs, affecting their day-to-day work.

Do - insure operational personnel are aware of the latest editions of the SOPs and where they can be located in their stability department (All SOPs on Site).

Do - insure they are able to refer to the SOPs for rapid guidance in performing their routine daily duties and tasks.

Do - insure supervisors and personnel have signed a '*Read and Understood*' form indicating full awareness of the SOP contents.

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DO'S AND DON'TS OF A STABILITY STUDY A DEPARTMENT TRAINING TOOL.

Do - insure SOP distribution is adequate and the SOPs Change Control System really works - and *on time*.

Do - monitor and approve proposed changes to Stability SOPs.

Do - insure the 25 ^{o}C *climatic* area for storing the ANDA and OTC stability samples at 25^{o}C ($\pm 2^{o}$) is a **controlled** environment room.

Do - insure access is through an controlled-access door, that does not affect the environmental temperature - every time the door is opened.

Don't - allow the stability room to be used as a stability office, where personnel are continually entering and leaving the controlled facility.

Don't - allow an air-conditioned 22^{o} -25^{o} C s*tability office* to function as a 25^{o} C climatic room.

Don't - store the 25^{o} C long term stability samples in an office.

(In terms of GMP compliance such a facility is inadequate and the environment cannot be controlled).

Don't - install unreadable chart temperature recorders due to the smallness of the rotating chart. (Reason: out-of-specifications temperatures are not adequately shown on the charts, as the range divisions on the chart are cramped and often too small. Narrow chart sensitivity scales are generally unsuitable and unreadable. The compliance value of such a temperature recording system is of minimal value and open to agency challenge).

Do - insist that current recording devices are fitted with larger chart recorder so that the daily temperatures and OOS values can be read with accuracy and precision.

Do - insure there is a system for 60% RH control (environmental humidity).

Do - insure the stability room has sufficient temperature probes at the *upper and lower* levels of the room where the stability samples are being stored.

Do - construct a dedicated stability room with controlled environmental facilities that maintain the temperature at 25^{o} C ($\pm$ 2^{o} C) and the relative humidity at 60 % RH ($\pm$ 5%).

Do - install the 30^{o} and 40^{o} C climatic chamber units *inside* the controlled stability areas or rooms.

Don't - allow stability samples for ANDA and OTC (development, or production samples) to be stored in cardboard boxes on cramped shelving (i.e. stacked one on top of the other. Drug Products need to be properly *exposed* to the controlled environment - this requires *orderly* storage on appropriate and spacious shelving. Products may not be stored indiscriminately in cardboard boxes). The samples are not exposed to the environment uniformly as they are protected by the insulating cardboard boxes in which they are stored.

Thus the lower samples are screened by the newer samples and a uniform controlled exposure to temperature and humidity is not generally achieved.

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DO'S AND DON'TS OF A STABILITY STUDY A DEPARTMENT TRAINING TOOL.

The older stability samples at the bottom of the cardboard box will be temperature and humidity screened by the several upper sample layers.

Do - avoid product exposure to large seasonal variations which do not keep the temperature in (non-insulated) stability rooms within a 2^{o} C range of 25^{o} C, in either winter or summer.

Do - avoid *uneven* room temperature *exposures* (near doorways, vents, fans.)

Do - insure the samples are arranged on the shelving in a neat, orderly manner.

Do - insure there is not a large *across* room-variation in temperature and humidity. Both these variables must be adequately controlled (< 5%).

Do - insure the upper and lower shelves have been challenged for temperature compliance. (A single chart recorder probe does not record the temperature accurately at which all the stability samples are stored. Multiple probes are necessary - i.e. > 2 upper and 2 lower.

Do - insure the room temperature validation studies have been conducted to insure the firm is aware of the actual storage parameters of the stability ANDA and OTC test samples.

Do - insure there is a substantive review and control of stability temperature *recorders or charts*.

Do - insure temperature / RH charts are reviewed for out-of-specification (OOS) temperature and RH values.

Do - insure the stability room charts are adequately signed and filed in an rapid retrieval system.

Do - insure adequate quality assurance evaluation is performed on the recording charts.

Do - insure there is corrective action taken when the stability temperature goes out of the specifications (OOS).

Do - insure that is possible for the firm to conclusively assure the FDA that the filed ANDAs were held at 25^{o} C, 40^{o} C ($\pm 2^{o}$ C) for the required storage periods of 3, 6, 9, 12, 18, 24, 36, etc. months.

Do - insure a corrective action SOP exists - to determine the procedures to follow after a failure of the recording equipment or power supply during an ongoing stability study.

Do - insure corrective actions are carried out, documented and *closed*.

Do - insure there are written emergency procedures for the use of *calibrated* hand-thermometers and recording logbooks due to recorder or stability probe failures.

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DO'S AND DON'TS OF A STABILITY STUDY A DEPARTMENT TRAINING TOOL.

Do - insure air-condition failures or equipment shutdowns are recorded.

Do - insure periodic revalidation and temperature distribution studies of the climatic chambers are carried out (every two years or when there is a change).

Do - insure Original Data Summary Sheets are never replaced with unauthorized "corrected versions".

Do - outlaw the use of "White-Out tapes or liquids" in stability and other reports.

Do - review of the annual report prepared for the FDA to show that the ongoing stability testing has been met, as per the filed ANDA commitment.

Agency Case-History I. - Data values go unrecorded.

Investigations highlighted that one set of data values had not been recorded. The appearance that the stability data sheets are a direct and accurate transfer procedure of the raw data in the laboratory notebooks is further open to question and investigation.

This technique appears to be used to alter raw data when the original worksheet data was not in compliance.

Case History II - Lost raw data

The 6 month data point for the product potency was required to be evaluated by microbial assay. However the raw data to support this assay value in the stability data sheet was not able to be found. Further investigation highlighted that this raw data was untraceable.

Do - insure there is no lost data and full *traceability* of stability test points.

Do - insure summary data sheets containing 'failed analysis results' are meticulously signed and filed.

Do - insure there exists a well documented reporting system for the **repeat** testing of stability data, according to written SOPs.

Do - insure traceability of ALL tests performed via the laboratory work-sheets, resulting in full credibility of the laboratory test results.

Do - investigate thoroughly if it appears that the stability data is tested and repeat tested *until* it passes.

Do - insure established procedures for investigating abnormal assay fluctuations or out-of-specification (OOS) results in the analytical and microbial stability testing program, is both operational and functional.

Do - insure OOS SOPs are written and the principles of the Judge Wolin's decisions are followed and properly investigated.

Do - review and audit stability documentation in order to establish the authenticity of the stability test results reported to the FDA in ANDAs, Supplements or Annual Reports. **I**nsure there is a *formal pre-submission* internal auditing program .

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DO'S AND DON'TS OF A STABILITY STUDY A DEPARTMENT TRAINING TOOL.

Do - insure the firms does verify the transfer of raw data values from the laboratory workbooks to the final computer stability print-out reports.
(Where *intermediate* summary sheets and analysis request forms are used, these intermediate data sheets should be *signed and stamped* as bona fide and accurate by Quality Assurance).

Do - insure the final stability study is signed off by the Director of Quality Control and the firm has a SOP specifying the *acceptance and sign-off* procedure for a completed stability study, to ensure that the study is complete and accurate.

Do - insure that no laboratory raw data is unavailable or missing in support of the Stability Summary Data Reports.

Do - insure proper *cross-referencing* of laboratory notebooks and worksheets with computerized documentation prior to data being submitted to the FDA.

Do - insure retrospective audits trails of ANDA stability reports to summary data sheets and back to laboratory workbooks clarify that the FDA filed data can be supported by the raw laboratory test data.

Do - insure the firm does have a comprehensive and functional laboratory data reporting system for test results.

Do - insure that data points are not missing (e.g. pH values; missing potency from crimp-end of semi solid tubes etc.).

Do - insure stability test values are not different from the filed values.

Do - insure the use of *bound and numbered* laboratory notebooks.

Note - The use of unnumbered analytical worksheets for recording analytical data should be discontinued and is not in GMP compliance.

Do - insure that stability data is not **selectively** screened prior to computerization.

Do - insure the absence of discrepancies and different values in ANDA Annual Reports and the original laboratory raw data.

[Case study:- Review of the annual report prepared for the FDA showed that the ongoing stability testing as per ANDA commitment showed an original report in the stability files with a test data line covered with "white tape". This data report was photocopied and sent to the FDA. The photocopy did not reveal the 'white-out' data in question.]

Do - insure traceability of workbook reference page numbers and dates relating to the original raw data in laboratory workbooks.

Do - insure the traceability of any repeat testing performed on the stability samples is clearly referenced on the stability documentation used to prepare the computerized stability reports.

Do - insure the need to prepare an SOP for cross-referencing laboratory notebook data with computerized stability test result documentation.

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DO'S AND DON'TS OF A STABILITY STUDY A DEPARTMENT TRAINING TOOL.

Do - insure all repeating testing performed at the same test interval must be cross-referenced - *all together*.

Note: a reviewer requires to audit *all* testing performed on the stability test sample and not only the raw data in the laboratory notebooks that *have passed* the stability check specifications.

Do - insure all stability data points are present and are in full compliance with the *pre-written* stability protocol.

Do - insure a full review of the stability protocol and a comparison of the test procedures carried out on the stability samples - at *each* test station - to highlight any incidence where stability data points may be absent or OOS.

Do - insure that no raw data is **omitted** from the stability reports or in the Annual Reports submitted to the FDA.

Do - insure stability SOPs are adequate and routinely reviewed for GMP compliance by written *in-house* audits.

Do - insure the existing SOPs do control the functions of the stability department. (45-50 Stability SOPs are a minimum prerequisite to operate a stability department for an innovative or generic drug manufacturing company).

Do - insure is that SOPs are not deficient both in the **content** and **detail.**

The lack of suitable SOPs in a stability department may result that much of the stability management and testing of the stability samples as erratic and *out-of-control* - resulting in a failed PAI review.

Do - insure that SOPs are readily available and routinely followed and updated (i.e. after a change or annually - The lack of a full set of stability SOPs and the fact that the SOPs are incomplete or that stability personnel are poorly trained on the contents of the SOPs is strong evidence to an agency that the firm's stability testing program is not in current GMP compliance).

Do - insure samples are analyzed on- time using; *First-In-First-Out* (FIFO).

Do - insure that it is not possible, for a sample in a stability program to remain untested after the 'due date' and thus skip the designated 'testing interval'.

Do - insure the Certificate of Analyses are not *out of date* for time zero when the sample is eventually placed on stability at a 'start date' several months after the initial C. of A. was performed.

[Reason - the sample assay value potency may have *degraded* by several months aging which would not be reflected by the *initial* certificate of analysis - some time earlier].

Do - insure the presence of stability SOPs controlling the maximum time period [30 days] between initial testing (Certificate of Analysis at time zero) and the 'Start Date' of the stability study in order not to invalidate the initial stability results.

Do - insure that all the stability SOPs are updated according to the firm's SOP index.

[End of Document]

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PHARMACEUTICAL STANDARD OPERATING PROCEDURES

Drug Development

I.A.G.I.M

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Standard Operating Procedures

This year 2001 SOP INDEX SUMMARY is intended for individuals or groups responsible for the management and operation of the generic drug development units. It is divided into four sections, pharmaceutical, analytical, microbiological and stability and equally valuable for the operation and control of the CMC (chemistry, manufacturing and control) section of a NDA researched-based unit.

All pharmaceutical companies conducting drug research and development must have SOPs. The primary purpose of the SOP is to translate the various regulations and guidelines, which are open to interpretation, into clear and concise sets of instructions.

Essentially generic development can be distilled into standard development procedures which any good drug developer would apply. A researcher conducts work according to a documented set of procedures - which hopefully represent the best and most current methods available i.e. drug development using “state-of-the-art” techniques.

A drug researcher must keeps a record of every detail of the product development - both the advances and the failures of the experimental batch lots. SOPs also demonstrate that you are following a key rule of a good researcher: The research procedures must be fully described in order that the methods can be duplicated and replicated as necessary by various unit personnel.

The Standard Operation Procedures chosen fully represent a cross-section of the SOPs needed for a drug development unit to operate efficiently and to produce drug products on time.

The updated index supplies all the major procedures required, while the selected 45 summary SOPs describe the purpose and the principles generally needed to meet the scientific, regulatory and at times GMP objectives of a well run stability unit.

Carefully written and structured SOPs will save research-based firms and generic developers both time and development dollars.

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SOP Number	Development Study Procedure:-
	SOP CONTROL
P-000-01-2001	Template for Pharmaceutical Development SOPs.
P-005-01-2001	Indexing procedure for Pharmaceutical Development SOPs.
P-010-01-2001	Index for Pharmaceutical Development SOPs.
P-015-01-2001	Signing procedures for Pharmaceutical Development SOPs.
P-020-01-2001	Numbering and format of Pharmaceutical Development SOPs.
P-025-01-2001	Circulation of Pharmaceutical Development SOPs.
P-030-01-2001	Annual Review of Pharmaceutical Development SOPs.
	DEVELOPMENT NOTEBOOKS
P-035-01-2001	Issue and use of pharmaceutical development notebooks
P-040-01-2001	Signing procedures for development notebooks
P-045-01-2001	Recording pre-formulation and development formula in development notebooks.
P-050-01-2001	Recording manufacturing instruction in development notebooks
P-055-01-2001	Recording IPQC specifications in development notebooks
P-060-01-2001	Recording finished product specifications in development notebooks.
P-065-01-2001	Review & auditing of pharmaceutical development notebooks
P-070-01-2001	Correction procedures in development notebooks & documentation
P-075-01-2001	Archiving of development notebooks.
	DEVELOPMENT QUALITY ASSURANCE
P-080-01-2001	Procedures For Development Change Control
	DEVELOPMENT FORMULA
P-085-01-2001	Operating procedures for product development.
P-090-01-2001	Formulation of ANDA topical preparations
P-095-01-2001	Formulation of ANDAs to Q_1Q_2 Status (semisolids)
P-100-01-2001	Validation requirements for Product Development
P-105-01-2001	Vendor Certification requirements for Product Development
P-110-01-2001	Check list for a pharmaceutical Development Report
P-115-01-2001	SOP for Development Reports

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P-120-01-2001	Formulation of **CR / ER** ANDA Oral Tablet Preparations
P-125-01-2001	Establishing an IVIVC in **E**xtended **R**elease *Oral Dosage Forms*
P-130-01-2001	Establishing a level A IN-VITRO IN-VIVO correlation
P-135-01-2001	Establishing a level B IN-VITRO IN-VIVO correlation
P-140-01-2001	Establishing a level C IN-VITRO IN-VIVO correlation
P-145-01-2001	Establishing a level A IN-VITRO IN-VIVO correlation
P-150-01-2001	Evaluating the predictability of a level A - IVIV Correlation
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	DEVELOPMENT REPORTS
P-160-01-2001	List of FDA Guidance documents impacting on product IR and CR development dosage forms.
P-165-01-2001	Setting up a general Development SOPs.
P-170-01-2001	Standard Procedures for Generic Product Development
P-175-01-2001	Setting up a *Product Specific* Development SOPs.
P-180-01-2001	*Product Specific* Development SOPs for CR Tablets - Contents.
P-185-01-2001	Setting up a *Product Specific* **ER** Development SOP.
P-190-01-2001	Setting up IVIVC for **E**xtended **R**elease *Oral Dosage Forms*
P-195-01-2001	Contents of a Development SOP - **ER** Oral Tablets.
	Active materials
P-200-01-2001	Active Drug Substances for Generic Drugs
P-205-01-2001	Developing Product Formula with approved Actives
P-210-01-2001	R&D Inventory Records for the Active Drug Substance
P-215-01-2001	Vendor Certification Requirements for Approved Actives.
P-230-01-2001	Decision tree for establishing impurity acceptance criteria.
P-235-01-2001	Decision tree for establishing degradation acceptance criteria
P-240-01-2001	Decision tree for establishing particle size acceptance criteria
P-245-01-2001	Decision tree for establishing polymorphism existence
P-250-01-2001	Decision tree for establishing microbiological testing
P-255-01-2001	Decision tree for evaluating chiral actives

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P-265-01-2001	Inventory Records for the Active Drug Substance.
P-270-01-2001	Investigating and handling abnormal batch results.
P-275-01-2001	Choosing the Antioxidant
P-280-01-2001	Antioxidant Qualification during Process Optimization
	Non-Active materials
P-285-01-2001	Non-active ingredients for ANDA formula development
P-290-01-2001	Use of Purified Water USP in Product Development
P-295-01-2001	Checking excipients in the FDA *'Inactive Ingredient Guide'*
P-300-01-2001	Evaluation and Requirements of Release Controlling Excipients
P-305-01-2001	Justification and functionality of the Release Controlling Excipient
	Container-Liner-Closure systems
P-310-01-2001	Container-Liner-Closure systems for Generic Development
P-315-01-2001	Documentation requirements for Container/Closure systems
P-320-01-2001	Check list for Container-Liner-Closure Documents
	In-process controls
P-325-01-2001	Choice of IPQC limits.
P-330-01-2001	Qualification of IPQC limits.
P-335-01-2001	Qualification of manufacturing process specification limits.
P-340-01-2001	In process control on bulk products
P-345-01-2001	Time limitations on manufacturing processing stages
	Finished Product Controls
P-355-01-2001	Choice of Finished Product Specification limits
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P-385-01-2001	Tablet lubricant Qualification during Process Optimization
	Process Qualification Batch
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P-395-01-2001	Side-by-side comparison for Process Qualification and Pivotal Batch
P-400-01-2001	Granule Content Uniformity Qualification
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P-415-01-2001	Check list of a TTD file
	Pivotal Batch
P-420-01-2001	Pivotal Batch requirements
P-425-01-2001	In-process sampling & testing procedures of tablets, caplets and capsules for pivotal batches
P-430-01-2001	Do's and Don'ts when preparing for pivotal batches
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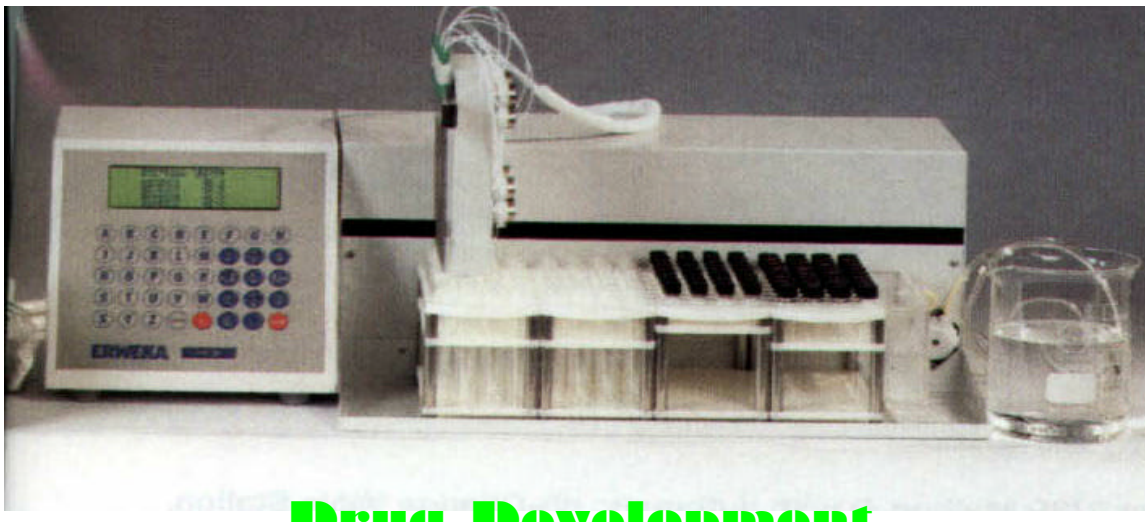

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A-020-01-2001	Circulation of analytical SOPs.
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A-030-01-2001	Reserved.
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A-**100**-01-2001	Receipt and logging-in of analytical laboratory samples
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A-**275**-01-2001	Assay determination by HPLC and GC methods.
A-**276**-02-2001	Assay determination by HPLC and GC methods -Details.
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A-390-01-2001	Pivotal Batch analytical requirements
A-395-01-2001	Do's and Don'ts when preparing for pivotal testing
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A-405-01-2001	Side-by-side analytical comparison for pivotal and validation batch
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A-**516**-01-2001	Calibration of pH meters
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A-**518**-0**2**-2001	Calibration of pH meters - Detailed
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A-520-01-2001	Annual qualification program for laboratory equipment
A-**524**-01-2001	Performance verification of Bausch & Lomb and Milton Roy spectrophotometers
A-**525**-01-2001	Spectronic Standards - Test Calibration Form # [001]
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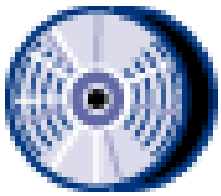

INDEX OF STABILITY SOPS

SOP Number Stability Study Procedure

The following *index* represents an adequate set of standard operating procedures for a stability department. In order for a stability department to function efficiently the principles described in these over +45 standard operating procedures are required to conduct a functional stability study. SOP examples are provided as a base. All SOPs listed are not provided.

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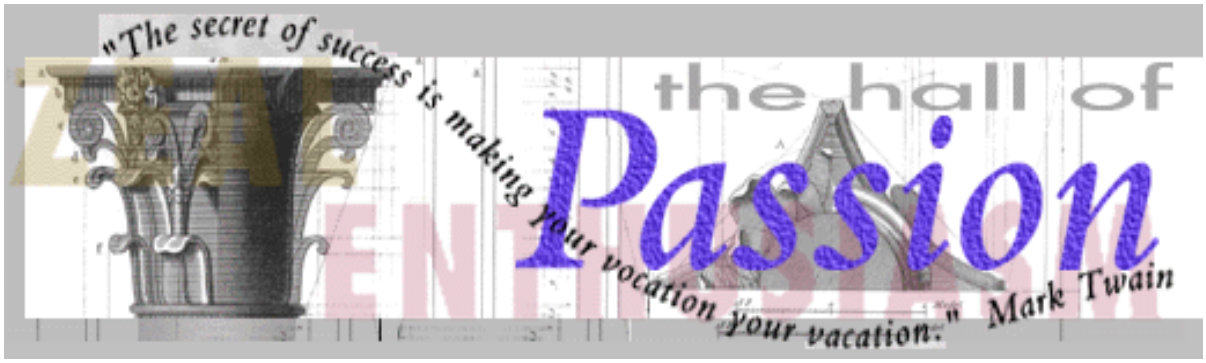

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AM-0240-0200-03

ANALYTICAL METHOD PROCEDURES

Total No of Pages: 4

ANALYTICAL METHOD
ASSAY AND RELATED SUBSTANCE DETERMINATION
HPLC Determination of 300mg Erdosteine Capsules

ASSAY of the MONTH

This assay is suitable for Erdosteine Capsules 300 mg as well as Erdosteine Suspension 175mg/5mL . No Erdosteine Assay has yet been published in the USP/NF or Pharmacopeial Forum.

HPLC ASSAY AND RELATED SUBSTANCE

Column	Eurospher 100, C18, 25 x 0.40cm 5µ
Mobile Phase	Buffer pH 2.0*: Acetonitrile (88 **:** 12 v/v)
* Buffer pH 2	Potassium dihydrogen phosphate (KH_2PO_4) - 0.68g
	Hepatane sulphonic acid - 1.01g
	Phosphoric acid (85%) - 4.6mL & Water to 1000mL adjust pH to 2.0 with Sodium hydroxide 10N (35% w/v)
Flow rate	1.0mL / min
Sample volume	10µL
Detector	UV at 220nm, AUFS 0.01

Mobile phase proportions and flow rate may be varied in order to achieve the required system suitability

ALL SOLVENTS USED MUST BE HPLC GRADE

ALL SOLUTIONS MUST BE FRESH DAILY

THIS ASSAY IS CURRENTLY NOT AVAILABLE IN THE USP24 / NF19 or PHARMACOPEIAL FORUM

STANDARD SOLUTION PREPARATION

Accurately weigh about 14mg of Erdosteine A.S. into a 50mL volumetric flask. Add about 35mL of mobile phase and sonicate to dissolve. Make up to volume with mobile phase. This is the standard solution.

SYSTEM SUITABILITY SOLUTION

Weigh about 6mg of Metabolite 1 into a 20mL volumetric flask. Dissolve in and make up to volume with standard solution.

AM-0240-0200-03

ANALYTICAL METHOD PROCEDURES

Total No of Pages: 4

ANALYTICAL METHOD
ASSAY AND RELATED SUBSTANCE DETERMINATION
HPLC Determination of 300mg Erdosteine Capsules

ED. N0: 04	Effective Date: IAGIM	APPROVED: SI - 10862 ERDOSTEINE 300mg CAPSULES #03 ASSAY AND RELATED SUBSTANCE FOR STABILITY STUDY			
Ed. Status : Supcds 03	10/01/2001	Anne	Bella	Edanna	Carol
		ANALYST	SUPERVISOR	QC	HEAD

AM-0240-0200-03

ANALYTICAL METHOD PROCEDURES

Total No of Pages: 4

ANALYTICAL METHOD
ASSAY AND RELATED SUBSTANCE DETERMINATION
HPLC Determination of 300mg Erdosteine Capsules

SYSTEM SUITABILITY TEST

Inject the System Suitability Solution. The retention time of the Erdosteine peak is about **6** minutes and of Metabolite 1 peak is about **7.5** minutes.

The resolution factor between these two peaks (calculated according to USP) should be not less than **2.5**.

The tailing factor of the Erdosteine peak (calculated according to USP) should be not greater than **1.5**.

A relative standard deviation, calculated for **5** replicate injections of standard preparation must be not more than **2.0%.**

SAMPLE SOLUTION PREPARATION

Weigh 20 capsules. Transfer as completely as possible the contents of the capsules to a suitable tared container and determine the average content weight per capsule. Mix the combined contents and accurately weigh about 60mg of the powder into a 200mL volumetric flask. Add 150mL of mobile phase and sonicate for 15 minutes. Make up to volume with mobile phase. Filter through a 0.45µ membrane filter.

PROCEDURE

Inject the Standard and Sample solutions into the chromatograph and determine the peak area of Erdosteine in each chromatogram with a suitable integrator.

CALCULATION

$$\frac{\text{Pk area smp} \times \text{Std wt}^{*}\text{(mg)} \times \text{Avg cap. cont. wt(mg)} \times 400}{\text{Pk area std} \times \text{smp wt(mg)} \times \text{Dose(mg / cap)}} = \%\ \text{Erdosteine of labeled claim}$$

* Std wt is corrected in accordance with % Assay and % Water.

CONTENT OF METABOLITE 1

During the HPLC determination of Erdosteine in capsules, the evaluation of Metabolite 1 can be done from the same chromatogram.

$$\frac{\text{Pk area Met 1}}{\text{Pk area Erdosteine}} \times \text{RF}^{*} \times 100 = \%\ \text{of Metabolite 1}$$

**RF = 4.0 - Response factor for calculation of Metabolite 1 =

$$\left(\frac{\text{Absorptivity of Erdosteine}}{\text{Absorptivity of Metabolite 1}} = 4.0\right)$$

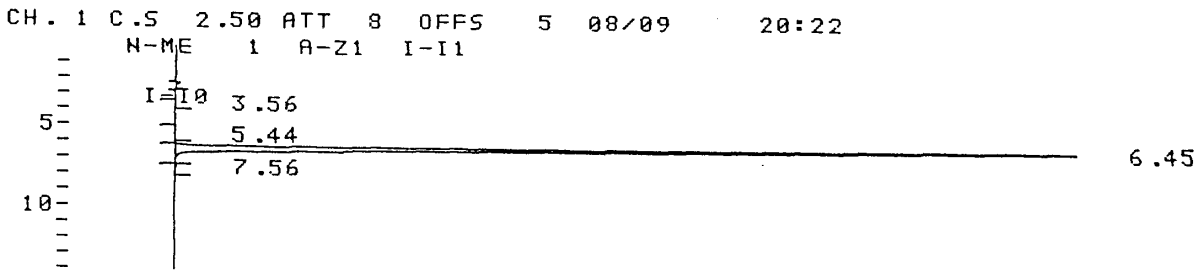
AM-0240-0200-03

ANALYTICAL METHOD PROCEDURES

Total No of Pages: 4

ANALYTICAL METHOD
ASSAY AND RELATED SUBSTANCE DETERMINATION
HPLC Determination of 300mg Erdosteine Capsules

TYPICAL CHROMATOGRAM



ERDOSTEINE ASSAY

Erdosteine Caps

SAMPLE: Erdosteine Capsules IAG-792

D-2500 08/09/9 20:22

METHOD: EN TAG: 12 CH: 1 VIAL: 16

FILE: 7 CALC-METHOD: AREA% TABLE: 0 CONC: AREA

NO.	RT	AREA	CONC	HEIGHT	BC
1	3.56	742	0.035	88	BB
2	5.44	4080	0.195	145	BB
3	6.45	2083062	99.538	215107	BB
4	7.56	4856	0.232	440	BB
TOTAL		2092740	100.000	215780	

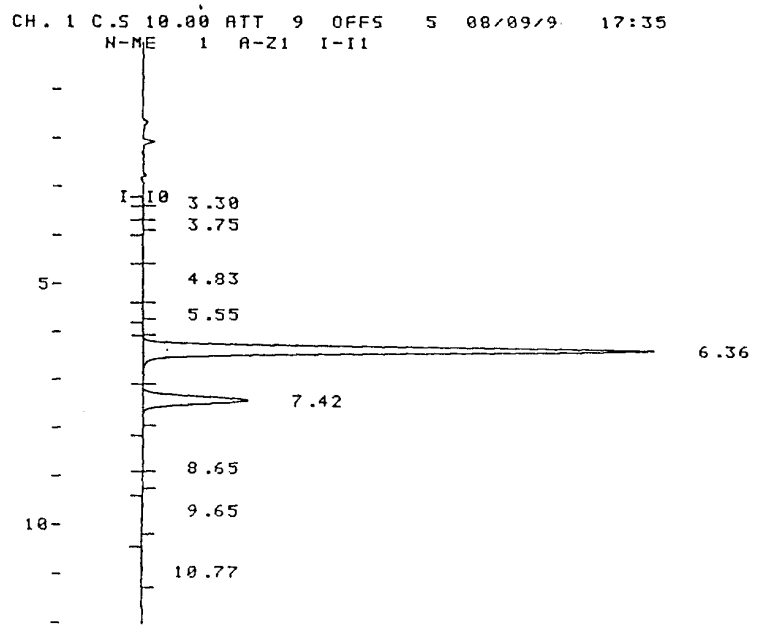
AM-0240-0200-03

ANALYTICAL METHOD PROCEDURES

Total No of Pages: 4

ANALYTICAL METHOD
ASSAY AND RELATED SUBSTANCE DETERMINATION
HPLC Determination of 300mg Erdosteine Capsules

SYSTEM SUITABILITY GRAPH



$$R = \frac{2 \times (7.42 - 6.36)}{0.30 + 0.30} = 3.5$$

$$T = \frac{0.30}{2 \times 0.12} = 1.25$$

ERDOSTEINE
ASSAY
SAMPLE: System Suitability

D-2500 08/09/9 17:35

METHOD: EN TAG: 1 CH: 1 VIAL: 11

FILE: 7 CALC-METHOD: AREA% TABLE: 0 CONC: AREA

NO.	RT	AREA	CONC	HEIGHT	BC
1	3.30	1332	0.036	228	BB
2	3.57	6327	0.171	920	BB
3	3.75	3552	0.096	645	BB
4	4.07	1504	0.041	154	BB
5	4.83	3910	0.106	245	BB
6	5.55	1014	0.027	108	BB
7	5.92	1127	0.031	146	BB
8	6.36	2954467	80.024	312006	BB
9	7.42	706609	19.139	63980	BB
10	8.65	3009	0.082	116	BB
11	9.03	2644	0.072	255	BB
12	9.65	4798	0.130	370	BB
13	10.77	1675	0.045	85	BB
TOTAL		3691968	100.000	379258	
PEAK REJ :		250			

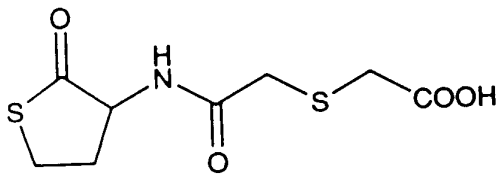
SOP # S-210-03-0600

ANALYTICAL METHOD PROCEDURES

Total Number of Pages 8.

ERDOSTEINE - MONOGRAPH.

STRUCTURAL FORMULA



(±1S-(2-[N-3-(2-oxotetrahydro thienyl)]acetamido)-thioglycolic acid)

$C_8H_{11}NO_4S_2$ M.W. = 249.307

DESCRIPTION

Color : White to ivory white

Appearance : Microcrystalline powder

SOLUBILITY

Slightly soluble in methanol, ethanol, acetone, water.

IDENTIFICATION

1. **Infrared Spectrum**

   The infrared spectrum of a nujol homogeneous dispersion of the test material, exhibits maxima only at the same wavelengths as that of a similar preparation of an Erdosteine A.S.

2. **HPLC**

   The retention time of the major peak in the chromatogram of the Sample preparation corresponds to that of the Standard Preparation, obtained as directed in the Assay.

PURITY TESTS

1. Appearance of solution

   A test solution (1.0% w/v in Methanol) is clear and colorless, according to E.Pharm. V.6.1.

2. Loss on drying

   Determined on a sample of about 1.0g, exactly weighed, in oven at 105°C up to constant weight, according to USP Method <731>.

   Specification: Not more than 1.0%

3. Residue on ignition

Determined on a sample of about 1.0g, exactly weighed, according to USP Method <281>.

Specification: Not more than 0.2%

4. Heavy metals

Determined on a sample of about 2g, exactly weighed, according to USP Method II <231>.

Specification: Not more than 0.001%

5. Chromatographic purity by HPLC (Limit Test)

The potential related substances most likely to be present are as follows:

- Homocysteine thiolactone (raw material)
- Homocysteine (coming from homocysteine thiolactone)
- N-chloro-acetyl-homocysteine thiolactone (RV 142) (synthesis intermediate)
- Thiodiglycolic acid (degradation impurity during synthesis)
- N-thiodiglycolyl homocysteine (Metabolite 1, corresponding to the Erdosteine cycle opening)
- Thioglycolic acid: (raw material)
- S-{2-[N-3-(2-oxotetrahydro thienyl] acetamido}-N(carboxymethyl thioacetyl)-homocysteine (RV 201) (synthesis secondary product)
- Bis N-(2-oxo-3-tetrahydrothienylthiodiglycolylamide (EP 21506) (Synthesis secondary product). (The presence of two peaks in the graph is due to the fact that EP 21506 is a mixture of 4 diastereoisomers).

- **THIS TEST SHOULD BE CARRIED-OUT AS RAPIDLY AS POSSIBLE.**
- **STANDARD SOLUTIONS SHOULD BE PREPARED PROMPTLY AND PROTECTED FROM LIGHT.**
- **THE MOBILE PHASE USED FOR MAKING DILUTIONS MUST BE EQUAL TO THE ONE PASSING ON THE COLUMN.**
- **THE USE OF AN AUTO-SAMPLER WITH REFRIGERATION IS RECOMMENDED.**

ERDOSTEINE - MONOGRAPH.

HPLC CONDITIONS

COLUMN	:	Eurospher 100 C18, 25 x 0.46cm, 5µ
COLUMN TEMPERATURE	:	30°C
MOBILE PHASE	:	Acetonitrile:Solution A* (11:89 v/v)
FLOW RATE	:	1.0mL/min
DETECTOR	:	UV at 220nm, AUFS 0.005
SAMPLE VALUE	:	20 µL

ALL SOLVENTS USED MUST BE OF HPLC GRADE

* Solution A - Buffer solution pH 2.0:

Dissolve 0.68g Potassium dihydrogen phosphate (KH_2PO_4) and 1.01g Heptane sulphonic acid in about 500mL water. Add 26.8mL of a 25% (w/v) Phosphoric acid and make up to 1L with water. Adjust to pH 2.0 with a 35% Sodium hydroxide solution.

Mobile phase proportions and flow rate may be varied in order to achieve the required system suitability.

Impurities stock solutions' and standard preparation:

Homocysteine Solution

Accurately weigh about 18mg ± 0.4mg Homocysteine into a 50mL volumetric flask. Dissolve in and make up to volume with mobile phase.

Homocysteine Thiolactone Solution

Accurately weigh about 18 ± 0.4mg Homocysteine Thiolactone into a 50 mL volumetric flask. Dissolve in and make up to volume with mobile phase.

Thioglycolic acid Solution (Mercaptuacetic acid)

Accurately weigh about 18mg ± 0.4mg Thioglycolic acid into a 50mL volumetric flask. Dissolve in and make up to volume with mobile phase.

Thiodiglycolic acid Solution

Accurately weigh about 18mg ± 0.4mg Thiodiglycolic acid into a 50mL volumetric flask. Dissolve in and make up to volume with mobile phase.

ERDOSTEINE - MONOGRAPH.

RV 142 SOLUTION

Accurately weigh about 12mg ± 0.3mg RV 142 A.S. into a 25mL volumetric flask. Dissolve completely and make up to volume with the mobile phase.

IMPURITIES DILUTED SOLUTION

Pipet 1mL each of the impurities stock solutions into a 25mL volumetric flask and make up to volume with the mobile phase.

ERDOSTEINE STOCK SOLUTION

Accurately weigh about 12mg ± 0.3mg Erdosteine A.S. into a 10mL volumetric flask. Dissolve in and make up to volume with mobile phase.

STANDARD SOLUTION

Pipet 1mL of the Impurities Diluted Solution and 4mL of Erdosteine Stock Solution into a 50mL volumetric flask and make up to volume with mobile phase.

The resulting concentrations of the impurities in this solution as percent of Erdosteine concentration are as follows:

Homocysteine - 0.3%
Homocysteine thiolactone - 0.3%
Thioglycolic acid - 0.3%
Thiodiglycolic acid - 0.3%
RV 142 - 0.4%

SYSTEM SUITABILITY TEST

Inject the standard solution and run the chromatogram up to 25 minutes. The peaks elute in the following order:

PEAK ORDER	RRT
Thiodiglycolic acid	0.52
Thioglycolic acid	0.60
Homocysteine	0.76
Homocysteine thiolactone	0.81
Erdosteine	1.0
RV 142	1.26

Typical retention time of the Erdosteine peak is about 6.2 minutes.

The resolution factor between Homocysteine thiolactone and Erdosteine peaks and between Erdosteine and RV 142 should be no less than 2.

ERDOSTEINE - MONOGRAPH.

SYSTEM SUITABILITY GRAPH

CHROMATOGRAM OF ERDOSTEINE SPIKED WITH THE IMPURITIES

SAMPLE SOLUTION PREPARATION

Accurately weigh about 30mg ± 0.6mg Erdosteine test material into a 25mL volumetric flask. Dissolve in and make up to volume with mobile phase.

Pipet 4mL of this solution into a 50mL volumetric flask and make up to volume with mobile phase.

PROCEDURE

Inject mobile phase (blank run). Inject the standard and sample solutions and run the chromatogram up to 25 minutes.

Determine the peak areas in each solution using a suitable integrator.

ACCEPTANCE CRITERIA

Subtract any blank peak from the sample solution chromatogram. No peak area in the sample solution chromatogram should be greater than that of the corresponding peak due to impurities in the standard solution chromatogram.

Calculate any other impurities such as

RV 201 - (RRT = 2.08),

Metabolite 1 - (RRT = 1.15) and

EP 21506 - (double peak at RRT = 3.23)

by means of area normalization.

ABSENT PEAKS - If no peak is detected at the corresponding RRT, report result as "Not detected" or "Less than the specified detection limit".

ERDOSTEINE - MONOGRAPH.

Specification

IMPURITIES	SPECIFICATIONS (UPPER LIMIT)	DETECTION LIMITS
Homocysteine	0.3%	0.25%
Homocysteine thiolactone	0.3%	0.15%
Thioglycolic acid	0.3%	0.15%
Thiodiglycolic acid	0.3%	0.15%
RV 142	0.4%	0.1%
RV 201	0.5%	0.1%
EP 21506	0.5%	0.02%
Metabolite 1	0.5%	0.01%
Single unknown impurity	0.2%	
Total	1.5%	

ERDOSTEINE - MONOGRAPH.

ASSAY BY HPLC

THIS TEST SHOULD BE CARRIED-OUT AS RAPIDLY AS POSSIBLE. STANDARD SOLUTIONS SHOULD BE PREPARED PROMPTLY AND PROTECTED FROM LIGHT. THE MOBILE PHASE USED FOR MAKING DILUTIONS MUST BE EQUAL TO THE ONE PASSING ON THE COLUMN. THE USE OF AN AUTO-SAMPLER WITH REFRIGERATION IS RECOMMENDED.

HPLC CONDITIONS

The same as for Chromatographic Purity (p.4).

STANDARD SOLUTION PREPARATION

Accurately weigh about 30mg Erdosteine A.S. into a 25mL volumetric flask, add about 20mL mobile phase and sonicate to dissolve. Make up to volume with mobile phase (standard stock solution). Dilute 4mL of this solution to 50mL with mobile phase.

SYSTEM SUITABILITY SOLUTION

Weigh about 6mg Metabolite 1 into a 50mL volumetric flask. Dissolve in and make up to volume with mobile phase. Pipet 3mL of this solution and 2mL of the Erdosteine standard stock solution into a 25mL volumetric flask and make up to volume with mobile phase.

SYSTEM SUITABILITY TEST

Inject the system suitability solution. The retention time of the Erdosteine peak is about 6.2 minutes. Metabolite 1 elutes at relative retention time of 1.15 related to Erdosteine.

The resolution factor between these two peaks (calculated according to USP) should be not less than 1.5.

A relative standard deviation calculated for 5 standard replicate injections must be not more than 2.0.

ERDOSTEINE - MONOGRAPH.

SAMPLE SOLUTION PREPARATION

Accurately weigh about 30mg Erdosteine test material into a 25mL volumetric flask, add about 20mL of mobile phase and sonicate to dissolve. Make up to volume with mobile phase.

Pipet 4mL of this solution into a 50mL volumetric flask and make up to volume with mobile phase.

Procedure

Inject the standard and sample solutions into the chromatograph and determine the peak area of Erdosteine in each chromatogram.

Calculation

1. Assay of Erdosteine:

$$\frac{\text{Pk area smp x Std wt * (mg) x 100}}{\text{Pk area std x smp wt * *(mg)}} = \text{\% Assay calculated on dry basis}$$

2. Assay of Metabolite 1:

$$\frac{\text{Pk area smp x Std wt * (mg) x Rf * * * (mg) x 100}}{\text{Pk area std x Smp wt * *(mg)}} = \text{\% Assay of Metabolite 1 calculated on dry basis}$$

* std wt - is corrected according to % Water and % Assay

** smp wt - is corrected according to % Water

*** RF = 4.0, response factor for calculation of Metabolite 1 = $\left(\frac{\text{Absorptivity of erdosteine}}{\text{Absorptivity of metabolite1}}\right)$ = 4.0

Specification

98.0% - 102.0% Erdosteine assay, calculated on dry basis.

PARTICLE SIZE

(This test is performed only for micronized active drug substance)

Apparatus : Computerized inspection system

Method : By volume distribution

Specifications : 100% less than 40µ

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VALIDATION OF PURIFIED WATER SYSTEM

A U D I T	DATA Complete	COMMENTS If data incomplete - state missing information
Validation Protocol Examine Master List of Protocols containing Edition Numbers and Effective dates of the Validation Protocols.	YES NO r q	
Review the Master Protocol List to ensure that the Validation Protocol's edition #. was the latest edition at the time of the validation run.	r q	
Validation Documentation Check that all pages are adequately filled out and signed and no pages are absent	r q	
Verify that all authorization signatures are in place and dated.	r q	
Installation Qualification Check that all pages are adequately filled out and signed and no pages are absent?.	r q	
Is the list of change controls of the equipment from last validation date updated?	r q	
Examine the list of instruments requiring calibration and check the: • Identification numbers of instruments. • Instrument Category • whether r Calibrated / r Not Calibrated.	r q r q r q	

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VALIDATION OF PURIFIED WATER SYSTEM

A U D I T	DATA Complete	COMMENTS If data is incomplete - state missing information
System Drawings Each drawing print has been verified as being correct and is suitably signed and dated	YES r NO q	
Operational Qualification Safety and Pressure Controls The results recorded comply with the system's specifications?.	r q	
pH Control The results recorded comply with the system's specifications?.	r q	
Conductivity Control The results recorded comply with the system's specifications?.	r q	
Tank (Tanks) Level Control The results recorded comply with the system's specifications?.	r q	
Tank Vent Filter Temperature Control and Monitor The results recorded comply with the system's specifications?.	r q	

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VALIDATION OF PURIFIED WATER SYSTEM

A U D I T	DATA Complete	COMMENTS If data is incomplete - state missing information
Reverse Osmosis / Purified Water Pump Flow Control Do all the results recorded comply with the system's specifications?..	YES r NO q	
PW Loop Flow Monitoring System Do all the results recorded comply with the system's specifications?	r q	
PW Loop Temperature Control and Monitoring Do all the results recorded comply with the system's specifications?.	r q	
SOPS VERIFICATION - (According to SOP Last Edition) Check that the appropriate SOPs are in place and are dated and signed.	r q	
SOP - Operating Instructions for the P/W System SOP - Preventive Maintenance of the P/W System	r q r q	
SOP - Sanitation of P/W System SOP - P/W System Daily Checklist	r q r q	
SOP - P/W System Repairs SOP - Maintenance and Replacement of Vent Filter for P/W System Check SOPs effective dates against the validation protocol's effective date	r q r q r q	

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VALIDATION OF PURIFIED WATER SYSTEM

A U D I T	DATA Complete	COMMENTS If data is incomplete - state missing information
Performance Qualification Chemical Tests Are all chemical tests are performed as stated in the protocol.	YES NO r q	
Check that all data is attached	r q	
Where Out-of-Specification Results have occurred, check that appropriate corrective action, as per written protocol, has been fully implemented.	r q	
Microbiological Tests Check that all tests are performed as stated in the protocol. Check that all data is attached.	r q	
Where Out-of-Specification Results have occurred, check that appropriate corrective action, as per written protocol, has been fully implemented.	r q	
Bacterial Endotoxin Tests Check that all tests are performed as stated in the protocol.	r q	
Check that all data is attached	r q	
Where Out-of-Specification Results have occurred, check that appropriate corrective action, as per written protocol, has been fully implemented.	r q	

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VALIDATION OF PURIFIED WATER SYSTEM

A U D I T	DATA Complete	COMMENTS If data is incomplete - state missing information
Final Report Check that all discrepancies are clarified in the Final Report.	YES r NO q	
Final Report is signed-off and the signature is dated	r q	
Have all discrepancies been followed up and signed-off and closed by the QA	r q	
All report pages are numbered and contain no "white-out or overwriting"?	r q	
The Final Report is signed-off by QA and signed as "complete and closed"	r q	

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Bacterial Endotoxin Tests

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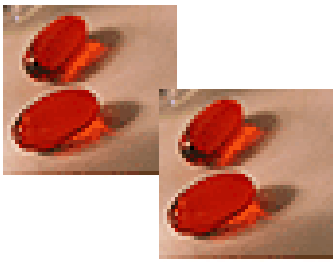

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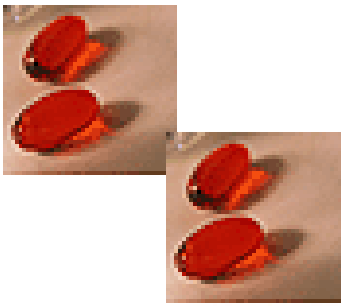

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