PRODUCT STABILITY TESTING PROGRAM - DESIGNING AND SUSTAINING NEW AND EXISTING PROGRAMS

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10:00 a.m. – 10:15 a.m.

Introduction to the Virtual Conference

Introduction to the Stability Testing Program

- **Why Perform a Product Stability Study?**
  - Chemical degradation of drug product leads to a reduction in the concentration of the active ingredient in dosage form.
  - Degradation of the drug product can lead to the formation of toxic products.
- **Evidence or Data of Testing Program Used to:**
  - Establish a product re-test period.
  - Establish a product's shelf life.
  - Establish adequate storage condition(s)
  - Determine a product's container closure system suitability.

Introduction to the Stability Testing Program

- **Purpose of the Stability Testing Program:**
  - Testing program provides assurance that manufactured products meets the defined or set specifications.
    - Throughout product shelf life.
    - Throughout testing period.
    - Product must be stored in accordance with their labeling instructions.
  - Testing program confirms assigned expiration date.
  - Provides evidence of a drug viability decay under the different environmental conditions.
  - Study must support product regulatory filings.

Stability Testing Program Applicability

- **Applicability of the Stability Testing Program :**
  - Applies to drugs in different phases such as:
    - Clinical Phase
    - cGMP Phase I
    - cGMP Phase 2
    - cGMP Phase 3
    - Commercialization

10:15 a.m. – 11:15 a.m.

Session 1

General Stability Considerations Applicable to a Product's Stability (I.e. Potency), Storage Conditions, Sampling Plan and Sample Handling

Key Discussion Topics

- ❑Regulations Guiding the Stability Testing Program
- ❑General Considerations Applicable to a Product's Stability Testing Program
- ❑Container and Closure Requirements
- ❑Storage Conditions (Temperature and Humidity)
- ❑Sampling Plan
- ❑Sample Handling
- ❑Choice of Analytical Assays/Tests and Specification

Session 1 – Learning Objectives

- **Regulations Guiding the Stability Testing Program**
  - Regulatory requirements of the program.
    - Delineating specific product types and associated requirements.
- **General Considerations Applicable to a Product's Stability Testing Program**
  - Stability Testing Program Submission Protocol for a New Drug Application
- **Container and Closure Requirements**
  - Applicable regulations guiding container and closure requirements
  - Container and closure requirements and considerations during a stability testing program.

Session 1 – Learning Objectives

- **Container and Closure Requirements contd.**
  - Verification or confirmatory tests of a product's container and closure.
- **Product Storage Conditions**
  - Guidelines associated with a product storage condition
  - Relationship of a product's storage condition and impact to its shelf life.
  - Types of products and stability program storage requirements.

Session 1 – Learning Objectives

- **Sample Handling in a Stability Testing Program**
  - Handling of products under a stability testing program
- **Stability Program Sampling Plan**
  - Performing an effective sampling plan.
  - Utilizing the appropriate sample size for a stability testing program.

Applicable Regulations and Requirements

- **21 CFR Requirements:**
  - **Section 512(b) of the Federal Food, Drug and** Cosmetic Act (21 U.S.C. 360b)
    - Establishes stability testing requirements for new animal drug approval.
  - **21 CFR 514.1**
    - Specifies the proper forms and the information required to be submitted.
  - **Section 514.1(b)(5)(x)**
    - Provides guidance about the applicants' role as follows:
      - Applicant's role in submitting data from a completed product's stability study.
      - Product's stability studies that are underway in order to substantiate the request for a specific expiration date.

Applicable Regulations and Requirements

- **21 CFR Requirements:**
  - **Section 514.1(b)(5)(x) contd.**
    - Provides information on the stability of the drug product.
  - 21 CFR Part 200 (cGMP regulations):
    - Provides guidance on cGMP requirements of the stability testing of products and its requirements.
  - 21 CFR 211.166
    - Provides guidance on the stability testing for pharmaceutical dosage forms
  - 21 CFR 226
    - Provides guidance on the stability testing for Type A Medicated Articles (medicated premixes)

General Considerations Applicable to a Product's Stability Testing Program

- **Stability Testing Program Submission Protocol**
  - One of the initial steps applicable to a new drug product.
  - Applicant can submit proposed plan prior to submission of original or supplemental NADA (New Animal Drug Application)
  - Applicant can obtain comments prior to committing to full stability testing or studies.
    - **Benefit:**
      - Provides ability to design and perform the program correctly.
      - Data becomes a permanent part of the NADA

General Considerations Applicable to a Product's Stability Testing Program

- **Stability Testing Program Submission Protocol**
  - Proposed Stability Program Testing Protocol:
    - Outlines specific clearly defined plans and items.
  - Stability Program Testing Protocol Considerations:
    - Draft a formal product stability protocol manner.
    - Include data packs
    - Include all statistical calculations, graphs and data trends.
    - Accompany stability testing packet with the final reports.

Stability Testing Program Submission Protocol for a New Drug Application

- **Typical Content of a Stability Testing Program Submission Protocol:**
  - ✓ **Submission protocol should be written adequately to effectively describe the following:**
    - Product Type
    - Sampling plan to be adopted
    - Duration of testing to be performed
      - Length of the stability testing program. i.e. 12 months, 24 months, 36 months etc
    - Frequency of testing to be performed
      - Stability time points for each identified test
    - Total number of samples to be used

Stability Testing Program Submission Protocol for a New Drug Application

- **Typical Content of a Stability Testing Program Submission Protocol:**
  - ✓ **Submission protocol should be written adequately to effectively describe the following:**
    - Total number of replicates per testing time interval
    - Storage conditions
      - Length,
      - Type,
      - Temperature,
      - Packaging
    - Describe the analytical methods to be followed
      - Compendia or in-house method etc
      - Reference of published methods and supporting data

Stability Testing Program Submission Protocol for a New Drug Application

- **Typical Content of a Stability Testing Program Submission Protocol:**
  - ✓ **Submission protocol should be written adequately to effectively describe the following:**
    - ❖ Active Ingredient of a Product
    - ❖ Drug Preparation
    - ❖ Strength (Potency)
    - ❖ Added Substances
    - ❖ Chemical and Physical Properties
    - ❖ Efficacy and Toxicity Studies
    - ❖ Product Changes
    - ❖ Degradation Products
    - ❖ Product Stability Parameters

Key Definitions Applicable to a Product's Stability

- **What is an Active Ingredient of a Drug?**
  - Has properties that confer pharmaceutical value to diagnosis, prognosis, prophylaxis, treatment, therapy.
- **Drug Preparation**
  - The active ingredient should be formulated in any drug preparation at 100% of label claim.
  - Justifiable overages are permitted but must not exceed the limits of:5
    - 5% for antibiotics
    - 3% for non-antibiotic chemicals.

Drug Potency – A Key Stability Indicator

Drug Potency – A Key Stability Indicator

- **Definition of a Drug Potency**
  - Pharmacological activity or strength of a compound.
  - A measure of drug's activity expressed as follows:
    - The amount required to produce an effect of a given intensity.
  - Used to determine the level of stability of the product's active ingredient.
  - Minimum acceptable potency level of a drug is considered to be 90% of the labeled potency.

Stable and Unstable Drug Product

- **Definition of Stable and Unstable Drug Product:**
  - **Stable Drug:**
    - Active ingredients which indicates drug potency is consistently stable.
    - Drug maintains the specified potency claim for the maximum anticipated shelf life
  - **Unstable Drug**:
    - Potency is reduced.
    - Impacts the safety of the drug
    - Results in the loss of efficacy as specified on the label.
    - In essence, the drug product is ineffective.

Added Substances in a Drug Product Where Applicable)

- **Definition of Added Substances (Where Applicable)**
  - Added to drug formulations to enhance the stability and usefulness of the drug.
  - Examples are absorbents and antioxidants.
- **Why Added Substances are Tested for Stability:**
  - Testing is based on the type of added substance
  - Testing is based on its relationship to the active drug ingredients.
  - Testing of the added substance may or may not be required.

Physical and Chemical Properties of a Drug Product

- **What are Physical and Chemical Properties of a Drug Product**
  - **Examples of Stability Related Tests:**
    - Physical Appearance
    - Solubility
    - Sterility,
    - pH
    - Viscosity
    - Disintegration Rate
  - Tests may be included in the stability testing program.

Physical and Chemical Properties of a Drug Product

- **Why a Product's Physical and Chemical Properties are Tested for Stability**
  - Proves a drug's stability:
    - Retention of chemical and physical properties are indicators of drug stability
- **Degradation Products:**
  - Presence or absence of harmful degradation products are measures of a drug's stability.
  - Important to test presence of such products during a stability testing program.
  - Include tests to measure presence or absence of degradation.
  - Where product degradation occur during product shelf life and storage:
    - Identify degraded products, investigate reasons and perform additional safety and efficacy studies.

Efficacy and Toxicity Studies and Stability Testing Program Requirements

- **Correlation between Stability Testing Program and Drug Efficacy/Toxicity Studies**
  - Stability study should be correlated with the following:
    - Efficacy and Toxicity Studies.
  - Performed on the final drug formulation whose efficacy and safety has been demonstrated.

Container and Closure Requirements During a Stability Testing Program

- **Applicable Regulations**
  - 21 CFR 211.94
    - Provides information to be used when considering containers and closures for products.
- **Considerations During the Early Development Stage:**
  - Selection of container and closure for a product should be supported by stability study results.
  - Acceptable to also use stability data of a comparable product type from internal or external client.
  - Evaluate data and provide rationale for acceptability and use.
  - Choice or path to be taken must be defendable.
- **Developmental Stability Study:**
  - Evaluate products in the container closure system representative of the clinical trial product.

Container and Closure Requirements During a Stability Testing Program

- **Containers and Closure Requirements for Clinical Trial and Commercial Product Stability Studies:**
  - Conduct studies using the following:
    - Products packaged in an identical container/closure system as clinical trial and commercial product.
  - Stability test sample packaging must contain the following:
    - The patient packet
    - IFU (Instruction for Use)
    - Compliance (i.e. If intended to be included in clinical marketing product, unless otherwise justified).
- **Containers and Closure Requirements for Formal Stability Study:**
  - Evaluate product in the *"to be marketed"* container and closure systems.

Container and Closure Requirements During a Stability Testing Program

- **Intended Market Container**
  - Product must be studied in its intended market container and closure
- **Container Material Integrity**
  - Container and closure must not interact with product.
  - Should prevent physical dissipation of the drug.
- **Containers for Liquids:** Product under stability study must adhere to the following:
  - Stored upright (i.e. in an inverted position) during the stability study.
    - Provides information on possible reactions between the product and containers, seals and caps.
- **Container Closure Integrity Test:**
  - Perform the integrity testing of the seal, torque fit, and leak of container and closures.

Container and Closure Requirements During a Stability Testing Program

- **Physical Observations of Container and Closures**
  - The container and contents should be inspected for physical observations, an unusual findings reported
- **Checks for Adhesive/Glue**
  - May need to conduct high temperature studies.
  - Test helps to evaluate the stability of adhesive properties of glue used in the manufacture of the container
- **Checks for Adequately Sealed Containers**
  - Perform seal integrity testing.
  - Perform for hermetically sealed products

Container and Closure Requirements During a Stability Testing Program

- **Changes to Container and/or Closures:** Requires the performance of a new stability studies:
  - **New Container or New Closure System:**
    - Use the first three (3) production lots.
    - The new system should be subjected to the ongoing stability studies.
  - **Changes to Material Composition of a Container or Closure:**
    - New stability studies for the impacted product stored within the modified container or closure needs to be performed.
  - **Changes in Container Size and Shape:**
    - Requirement for new stability studies will be determined during the review of the NADA supplement.

Guidelines and Consideration of a Product's Storage Condition

- **Guidelines of a Product Storage Condition:**
  - Apply basic scientific principles
  - Follow ICH guidelines
  - Follow other regulatory guidelines
  - Best practices and as appropriate.
- **Considerations Associated with a Product Storage Condition:**
  - Condition must mimic how the product will be stored.
  - Condition must mimic how the product will be transported
  - Storage chambers must be controlled/monitored to:
    - Ensure that product stability study is conducted within the required temperature and/or humidity conditions
  - Excursions from required storage conditions must be investigated, documented and impact determined.

Relationship between Product Storage Condition and Shelf Life/Expiry.

- **Applicable Regulations Guiding Product Shelf Life/Expiry**
  - 21 CFR 211.137 and 211.166
    - Pharmaceutical dosage forms.
  - 226.58(d)
    - Type A medicated articles of the cGMP regulations.
- **Definition of a Product's Shelf Life or Expiration Date**
  - Time period from the product manufacture date, through administration and until the product can no longer be used (i.e. Ineffective)
- **Relationship between an Effective Stability Study and Impact to Shelf Life Determination:**
  - Helps to reduce erroneous shelf life determination:
    - Accuracy in stability test data helps to establish an accurate product's shelf life/expiration date.

Relationship between Product Storage Condition and Shelf Life/Expiry.

- **Relationship between an Effective Stability Study and Impact to Shelf Life Determination:**
  - Statistical analysis from stability testing data and trending may be used to propose a tentative shelf life/expiry (extrapolation) for the product.
  - Tentative expiration date may be based on pilot batch data
  - Tentative expiration date can be adjusted based on data from production lots.

Shelf Life Duration of Studies and Expiration Dates (Generation of Shelf-Life)

- **Product's Shelf Life Determination:**
  - Determined using **Aging Studies** and **Formal Stability Study** Data from the following:
    - Drug Product.
    - Drug Substance
    - Novel Excipient
  - The shorter of the drug product, drug substance or novel excipient's stability.
  - A product's shelf life can be extended based on the following data:
    - Formal Stability Program
    - Annual or Primary Stability Program.
    - Performed for products with the same comparable final formulation and/or relevant stability studies.

Stability Testing Program Sample Requirements

- **Types of Production Samples for Stability Testing Program:**
  - **Production-size Batch or Lots**
    - Preferable to use samples or products from production-size (batch) for stability studies.
      - Report if pilot batch samples are used instead of production size samples.
  - **Use of Laboratory Scale Samples:**
    - Provides for optimum control of all factors.
    - After drug approval, "real" or "actual" use situations will have to be monitored and evaluated, resulting in changes to specifications.
    - Report all such changes to the Agency.

Stability Testing Program Sampling Plan

- **Requirements of an Effective Stability Testing Program Sampling Plan**
  - Plan must be representative of the manufactured batch or lot.
  - Frequency of sampling/number of samples taken per time period determined as follows:
    - Justifies the sampling frequency
    - Justifies the number of samples taken.
      - **Note:** Greater variability of some assays may necessitate an increase in the number of samples needed at each time period.

Stability Testing Program Sample Handling Requirements

- **Handling of Stability Test Samples**
  - Establish the initial data point
  - Analyze samples as soon as possible
    - If possible, at the completion of manufacturing (on the same day is more desirable).
  - Samples not tested on the same manufacture date are:
    - Placed in moisture-proof, air-tight containers.
    - Sample handling containers are tightly sealed to minimize entry of air as much as possible.
  - Store at 0°F or at a chosen temperature to reduce the following:
    - Any chance of degradation
    - Mold growth
    - Chemical action.

Stability Testing Program Sample Handling Requirements

- **Handling of Stability Test Samples**
  - Samples shipped to be Tested by an Outside Testing Laboratory are:
    - Properly labeled and packaged
    - Samples should be tested upon receipt prior to their introduction into the respective stability program
- **Stability Storage Conditions and Testing Schedule:**
  - Represent conditions under which the product will be stored and tested.
  - Test should help to establish a stability profile for the product.

Stability Testing Program Routine Testing Schedules

- **Recommended Testing Schedules**
  - Recommended that stability testing be performed per assigned schedule and as follows:
    - Time Zero
    - Every 3 Months = Year #1
    - Every 6 Months = Year #2
    - Every 12 Months = Annually
    - More frequent testing near the end of the anticipated expiration date may give a better information about the actual stability of the finished product.
  - Perform all the pertinent stability tests such as:
    - Physical, chemical or microbiological.
    - Results are to be reported as per the stability reporting commitment.

Stability Testing Schedule

Table 1: Suggested Testing Schedule for Room Temperature Testing

Proposed Expiration Date	Test Schedule for Room Temperature Testing Room Temperature: 25°C
6 months	0 (Initial),2,4,6 mos.
1 year	0 (Initial),3,6,9,12 mos.
18 months	0 (Initial),3,6,9,12,18 mos.
2 years	0 (Initial),3,6,9,12,18,24 mos.
3 years	0 (Initial),3,6,9,12,18,24,36 mos.
4 years	0 (Initial),3,6,9,12,18,24,36,48 mos.
5 years	0 (Initial),3,6,9,12,18,24,36,48,60 mos.

Stability Testing Schedule

Table 2: Suggested Test Schedule for Elevated Temperature Testing

Proposed Expiration Date	Test Schedule for Elevated Temperature Testing Elevated Temperatures: 37-40°C
6 months	0 (Initial), 2, 4, 6 months.
1 year or greater	0 (Initial), 3, 6, 9, 12 months.

Stability Testing Schedule

Table 3: Suggested Test Schedule for Additional Temperatures

Type of Temperature	Test Schedule
Refrigeration Temperature: 2°C - 8°C	Schedule and length of anticipated storage period (expiration date) under these conditions will depend on nature of the product, active ingredient and/or other related factors
Freezing Temperature: 0°C or below	0(initial).....up to 7 days
Reconstituted Products	Time element and schedule will depend upon nature of product, active ingredient, proposed expiration date and/or other related factors. Example; powder held for 14 days should be tested as follows: 0(initial),3,7,11, and 14 days.

11:15 a.m. – 11:30 a.m.

Break

11:30 a.m. – 12:30 p.m.

Session 2

Designing and Conducting Effective Stability Testing Program Using the Suggested Schedules for Various Product Types

Key Discussion Topics

- ❑Performing Pre-approval and Post-approval Studies
- ❑Performing Different Types of Temperature Studies
- ❑Stability Schedules Based on Different Types of Products
- ❑Special Humidity Considerations

Session 2 – Learning Objectives

- **Pre-approval and Post Approval Stability Testing Studies**
  - How to conduct such studies
- **Types of Temperature and Other Studies**
  - Reformulated Products
  - Accelerated Stability Studies
  - Temperature Studies
  - Room Temperature Studies
  - Elevated Temperature Studies
  - Refrigeration Stability Studies
  - Freezing Temperature Studies
  - Special Humidity Considerations
  - Others.

Session 2 – Learning Objectives

- **Suggested Stability Schedule and Time Points for Different Product Types Based on Regulations**
  - Based on Product Types, regulations and other considerations
  - Suggested time points based on product type:
    - Solid Dosage Forms Suggested Test Schedule
    - Liquid and Semi-solid Types Products Suggested Test Schedule
    - Reconstituted Products Suggested Test Schedule

Types of Stability Studies

- **Types of Stability Studies:**
  - Pre-approval Stability Studies
  - Post-approval Stability Studies
- **Pre-approval Stability Studies:**
  - Performed prior to approval of the drug product for use, propose a stability schedule.
  - Schedule is submitted with the stability commitment for review.
  - Test at least 3 lots of product of a typical batch size.
- **Post-approval Stability Studies:**
  - Designed to ensure or verify the adequacy of the pre-approval stability testing data.
  - Verifies that the change from pilot to production lot has not introduced any unknown variable or has been influenced by any unforeseen problems.

Reformulated Product Stability Studies

- **Reformulated Products**
  - This is a product whose formulation has been modified.
  - Reformulated products are considered new products
  - The change in the formulation needs to be verified that it has not affected the stability of the drug.
  - When reformulated, a product:
    - Must be subjected to the original product stability schedule and testing.
    - All stability testing program must follow the same guidelines as stated by the regulations for the product.

Elevated Temperature Studies

- **Elevated Temperature Studies**
  - Studies the impact of stress caused by higher temperatures.
  - These studies are performed for:
    - Pharmaceutical Dosage Forms
    - Types A, B, C Medicated Feed Preparations
  - Elevated temperature is 37°C to 40°C
  - Elevated temperature studies are for a shorter time period.

Accelerated Temperature Studies

- **Accelerated Temperature Studies**
  - Conducted when necessary to provide information for a prediction of a tentative expiration date of the product.
    - The product is stored at elevated stress conditions.
    - Degradation at recommended storage conditions is predicted based on:
      - The degradation at each stress condition
      - The known relationships between the acceleration factor and the degradation rate.
    - A product may be released based on accelerated stability data. However, the real-time stability testing must be done in parallel to confirm the shelf-life prediction.

Accelerated Temperature Studies

- **Accelerated Temperature Studies**
  - Best to design program carefully to reduce prediction errors.
  - Best to store several production lots at various acceleration levels to reduce prediction error.
  - Temperature is most common acceleration factor used for chemicals, pharmaceuticals, and biological products.
  - Relationship of temperature with the degradation rate is well characterized by the Arrhenius equation.
  - Equation describes a relationship between temperature and the degradation rate as in Equation 4.

Room Temperature Studies

- **Room Temperature Studies (Room Temperature is *25*°C)**
  - These studies are performed for the following as an example:
    - Pharmaceutical Dosage Forms
    - Types A, B, C Medicated Feed Preparations
  - The FDA's position is that:
    - It is acceptable to combine data compiled at room temperature and at accelerated temperature to justify an expiration dating period of over two years as follows:
      - By taking a sample product that has been at room temperature for one year and subjecting that sample to accelerated temperature conditions.
      - The expiration dating period will be the sum of the justified form individually at each storage condition

Refrigeration Temperature Studies

- **Refrigeration Studies:**
  - Performed on products requiring:
    - Refrigeration after opening
    - Refrigeration after reconstitution
  - Test unused portions of opened containers

Freezing Temperature Studies

- **Freezing Temperature Studies:**
  - Freezing studies performed on:
    - Liquid and semi-solid preparations
  - Observe the occurrence of precipitates during freezing and during thawing
  - Determine toxicity and safety of any precipitates
  - Perform normal stability tests on product after freeze test period to insure product has not degraded.

Ambient Temperature Studies

- **Ambient Temperature Studies**
  - These studies are performed on:
    - Products exposed to natural existing temperatures.
    - Medicated feeds, blocks or liquid feeds which are used outdoors and exposed to natural temperatures.
  - Products are studied under a similar natural environmental conditions which they are typically exposed.
  - Report minimum and maximum existing weather conditions.
  - Report temperatures at the time of sampling and testing.

Special Humidity Considerations

- **Special Humidity Considerations**
  - Preparations requiring a special humidity environment should include:
    - The amount of humidity with the temperature schedule under study.

12:30 p.m. – 1:30 p.m.

Lunch

1:30 p.m. – 2:30 p.m.

Session 3

Stability Testing Protocol Design, Data Management, and Trending. Comparative Analysis of Using a Manual versus Automated Data Management

Key Discussion Topics

- ❑Stability Protocol Design
- ❑Data Management, Trending and Statistical Analysis
- ❑Generation of Product Shelf Life or Expiry Date
- ❑Use of Extrapolation of Stability Test Data
- ❑Various Statistical Methodologies of Performing Data Trending and Extrapolation
- ❑Management of Stability Testing Data - Manual Versus Automated Software

Session 3 - Learning Objectives

- Designing an effective Stability Testing Program, Protocol and a Report for a New and Existing Product
- How to Effectively Handle, Manage Data, Utilize and Perform the Trending of Stability Testing Results and Data.
- Using Stability Testing Data to Generate the Product's Expiration Dating or Shelf Life.
- How to Perform the Extrapolation of Data to Predict a Product's Shelf Life (from an Ongoing Stability Testing Program – Great for products in clinical studies).
- Various ways of performing statistical analysis of the stability test result data (manual versus automated software).
- Advantages and Disadvantages of Manual and Electronic Data Management Software

Designing an Effective Stability Testing Protocol

- **The Stability Testing Program Protocol Design Process**
  - Performed at the onset of the determination of the need of a stability study .
  - A stability study protocol must be formally written.
  - All stability studies require a pre-approved protocol.
  - An effective and well designed stability protocol includes the following information:
    - Purpose of the study
    - General description and background information of the study object
      - Drug Product
      - Drug Substance
      - Excipient
    - Rationale for selection of a specific stability lot

Designing and Effective Stability Testing Protocol

- An effective and well designed stability protocol includes the following information:
  - Storage Conditions
  - Study Duration
  - Retest Date (where applicable)
  - Retest Period (where applicable)
  - Scheduled Pull Date
  - Pull Date
  - Testing Frequency
  - Test Attributes
  - Test Methods
  - Acceptance Criteria

Requirements of a Product Stability Lot

- Description of the requirements are not limited to the following:
  - Manufacturing process requirement
  - In-process and lot release testing requirements
  - Raw materials for drug product lot build
  - Acceptable temperature range during transportation of stability samples prior to the stability study (if applicable)
  - Description of the container closure system
  - Sampling plan

Drafting an Effective Stability Program Trend Report

- **Drafting an Effective Stability Program Trend Report**
  - A Stability testing program trend reports is used to:
    - Discuss the welfare of the product welfare.
    - Provide a rationale for establishing a product's expiration date using the data from testing.
    - Discuss previously set expiration date for an existing product (to make modifications. i.e. extensions)
      - A product's expiration or shelf life is extended using statistical analysis from extrapolated data and trend information.

Drafting an Effective Stability Program Trend Report

- **Content of the Stability Trend Report**
  - Discuss the results that were generated for the period.
  - Trend each individual attributes.
    - Trended data should be included in the report
  - Shelf life and potency requirements are discussed.
  - Determine the product's expiration date or shelf life based on the data.
  - Provide graphical representation of the individual test data.
  - Provide a trend of each individual test result over time.
  - Discuss any discrepancies and out of specification results.
  - Discuss any impact to the program
  - Provide a conclusion based on the data analysis.

Importance of Stability Test Data

- **Importance of Stability Testing Data**
  - Provides a picture of the product's conformity over the duration of claimed expiry.
  - Provides a picture of the product's stability over the duration of claimed expiry.
  - Provides a confidence level that the product is consistently meets the claimed potency, sterility or other stability indicators.
  - Data is important for expiration date projection.
  - Continuous data is important for extended expiry (if proven) past original claimed expiry.

Predicting a Product's Shelf Life/Expiry

- **Extrapolation of Stability Testing Data:**
  - Extrapolation of stability test data from time points may be used to:
    - Predict, define or extend the product's, drug substance or novel excipient's shelf life or expiry.
    - Should be based on the requirements in ICH Q1E, Evaluation of Stability Data"
- **Routine re-visit of stability data based on time points and expiry.**
  - Checks for conformity to the assigned expiration date.
  - Modification of expiry date as time points data are added to trend.
  - Useful in determining products with no previous history or comparable.

Choosing a Stability Testing Program Software

- **How to Choose a Good Stability Program Software**
  - The best choice of a software has the following attributes:
    - Ease of Interpreting the Stability Data.
    - Meaningful to the Operation.
    - Effectively analyzes test data to provide a confidence level in determining a product's expiry using the data.
    - Provides an upper and lower confidence level.
    - Ease of validation of the software.
    - Provides a pictorial representation of data using different graphical representations.
    - Provides a meaningful trend throughout the stability program period.

Considerations When Choosing a Stability Testing Program Software

- **Use of Critical Stability Indicators (What to Consider)**
  - Product potency data is very critical
- **Statistical Analysis Approach**
  - Application of Confidence levels (Upper Level versus Lower Level)
    - 95% Confidence Level
    - 80% Confidence Level
  - Confidence Level based on product type and available data.

Considerations When Choosing a Stability Testing Program Software

- **Routine Re-visit of Stability Testing Data**
  - This is based on time points and expiry.
  - Helps to check for conformity to the assigned expiration date.
  - May be used to modify a product's current expiry date as time points data are added to trend.
  - Useful for making decisions for products with no previous history or comparables.
- **Routine Stability Trend Reports**
  - Discusses a product's welfare based on a previously set expiration date.
  - Important to provide a picture of the product's performance in a snap shot.

Stability Testing Data Documentation, Entry and Management

- **Data Documentation, Entry and Management (Types of Documentation Methods):**
  - **Manual Documentation Method:**
    - Use of paper testing forms.
  - **Automated Software Documentation Method:**
    - Data is directly entered into the LIMS system.
  - Benefits and Shortfalls of Each Type of Method
- **Stability Testing Data Management Process:**
  - Use of LIMs for Data Entry, Analysis and Reporting
- **Critical Statistical Parameters and Methods**
- **Data Trending:**
  - Importance of a Stability Trend Report

Disadvantages of Each Type of Stability Testing Data Management System

- **Disadvantages of Each Type of Data Management System**
  - **Manual Data Entry and Management System:**
    - Cumbersome process.
    - Extensive documentation and test data management and approvals.
    - Human errors during statistical analysis.
    - Difficult to see a clear picture of the products performance in one shot.
    - Time consuming process
    - May sometimes be inefficient
    - Lost data and/or documentation associated with the paper trail
    - May pose a delay in data analysis and trending
    - Difficult to use for a multi-product operation and testing program

Disadvantages of Each Type of Stability Testing Data Management System

- **Disadvantages of Each Type of Data Management System:**
  - **Automated Data Entry and Management System (LIMS):**
    - Initial Expense and Cost (Based on the Type)
    - Requires a validation period and expense
    - Must be 21 CFR Part 211 compliant
    - Extended initial set up period

Advantages of Each Type of Stability Testing Data Management System

- **Manual Data Entry and Management System:**
  - Minimal set up cost when compared with automated software
  - Easy and speed of the initial set up
  - Okay to use for a single product operation
- **Automated Data Entry and Management System (LIMS):**
  - Eliminates manual/redundant processes.
  - Harmonizes core business processes and standardization of data.
  - Data has an audit trail (chain of custody).
  - Increases productivity associated with data turn around time.

Advantages of Each Type of Stability Testing Data Management System

- **Automated Data Entry and Management System (LIMS):**
  - Improves stability trend data and reporting process
  - Accuracy in determining the product's expiration date/shelf life.
  - Provides assurance using statistical analysis and confidence level.
  - Eliminates validation issues associated with use of excel spreadsheets.
  - Provides a picture of the product throughout its expiry and extended expiry date.
  - Improved Regulatory compliance; No 483s

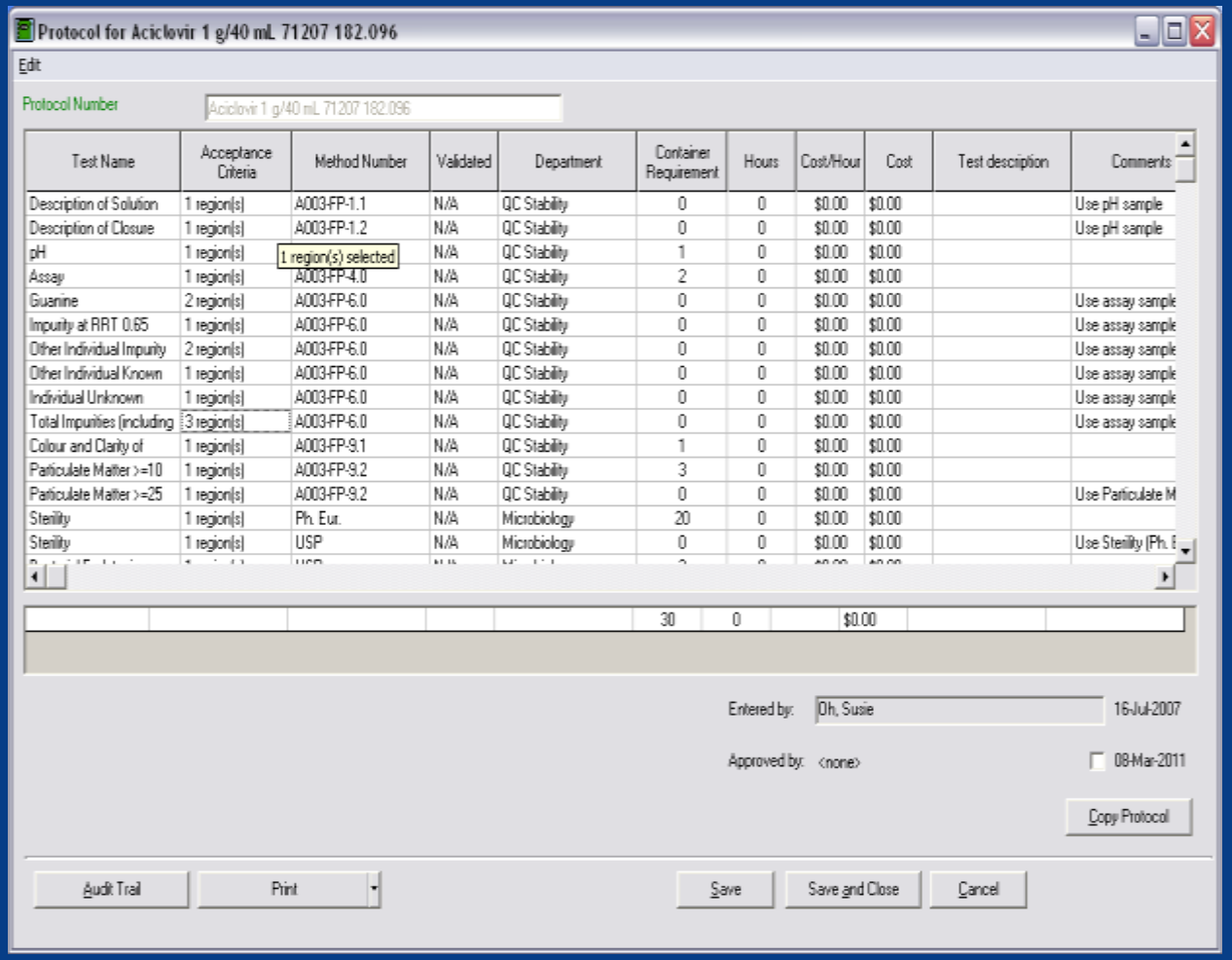
Advantages of Each Type of Stability Testing Data Management System

- **Automated Data Entry and Management System (LIMS):**
  - Ease of compiling and accessing test data.
  - Turns test data into a meaningful information for each testing time point.
  - Turns information into meaning information and scientific knowledge.
  - Alleviates the complexity of managing extensive stability test data:
  - Extensive information captured throughout study execution is critical to compliance.

Advantages of Each Type of Stability Testing Data Management System

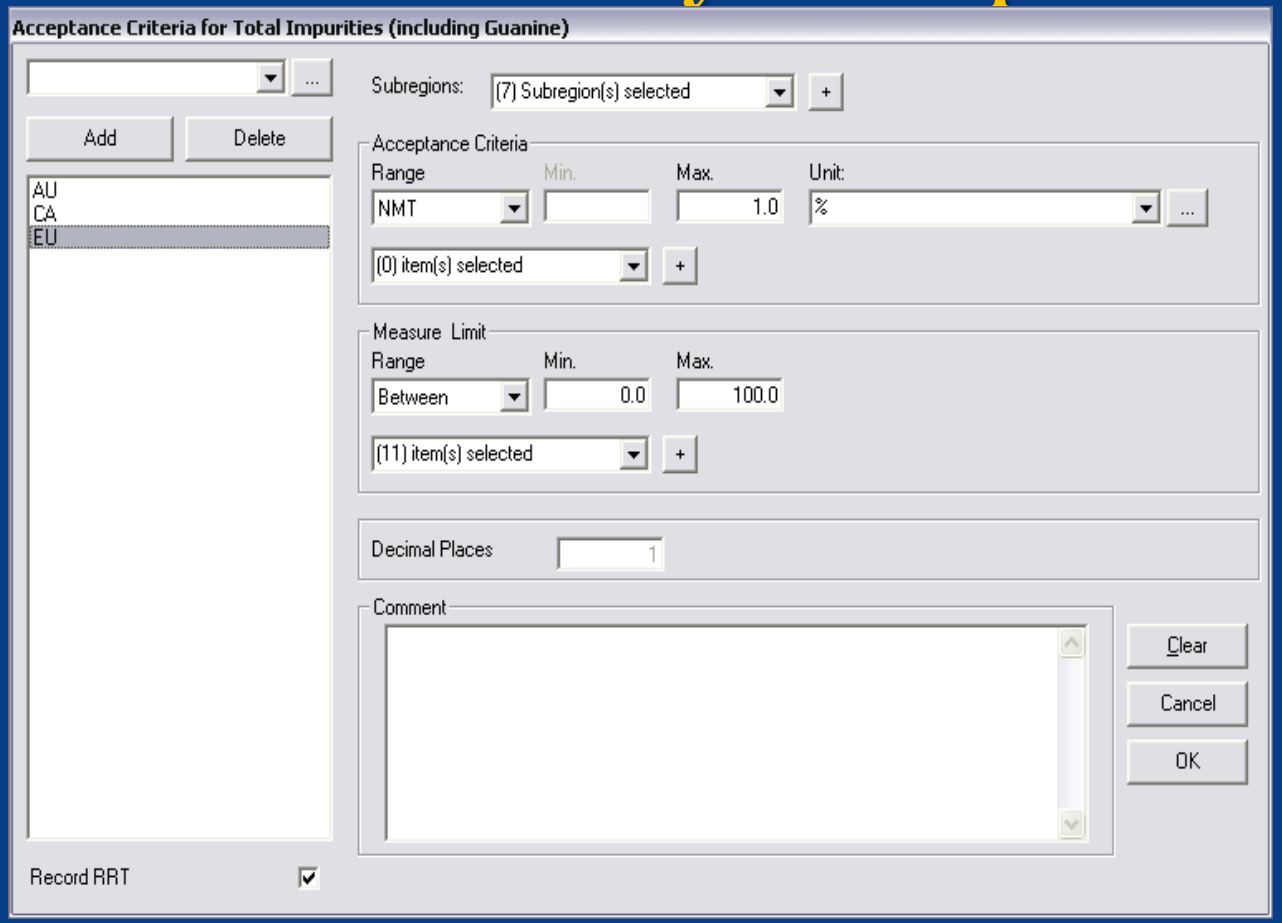
- **Automated Data Entry and Management System (LIMS):**
  - Used to support a complex set of compliance activities in the highly regulated pharmaceutical environment.
  - Provides the ability to achieve process excellence throughout the stability program.
  - Used to efficiently trend stability data
  - Investigation of stability testing OOS
  - Enhanced data query and mining
  - Data is managed and contained in one system.
  - All data can be easily analyzed expediting problem detection
  - Improves data integrity and security
  - Provides a state of control of the stability program

Example of a Screen Shot of a LIMS Stability Module - Protocol



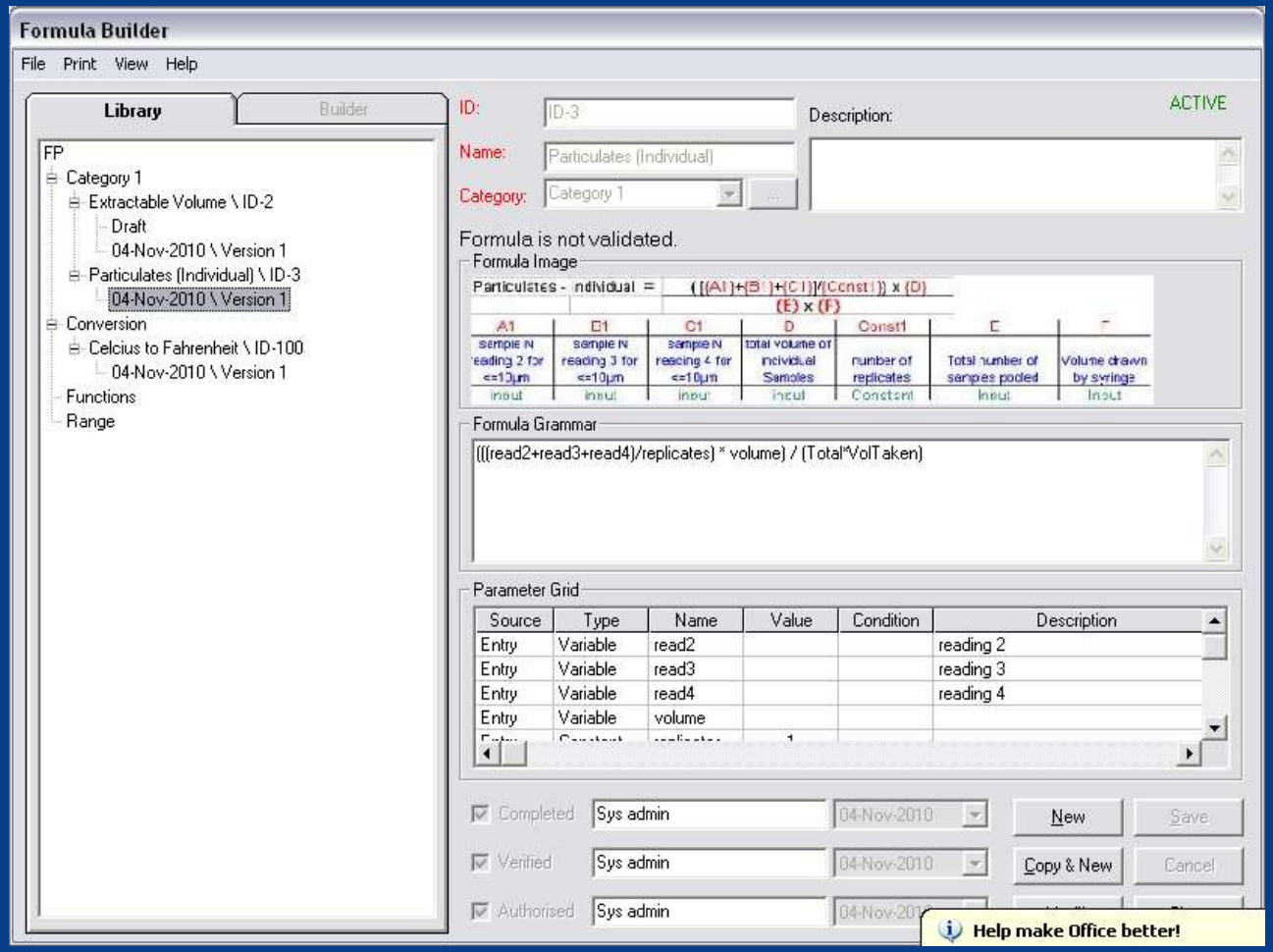
1. Permits multi-stage testing.
2. Has the ability to copy records to accelerate data entry
3. Include fields for details regarding testing criteria

Example of a Screen Shot of a LIMS Stability Test Specifications



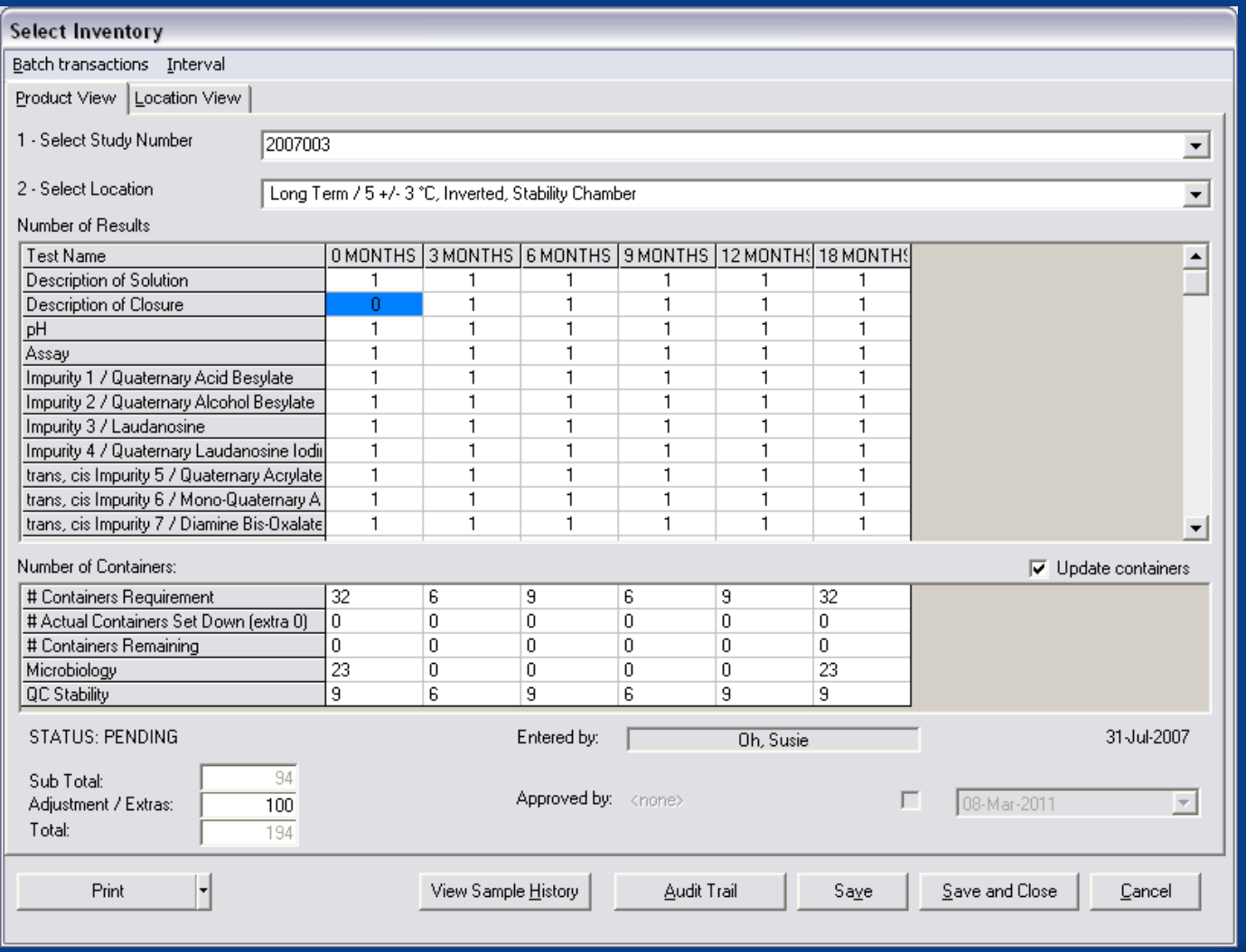
1. Has fields for details regarding testing criteria
2. Permits multi-stage testing
3. Has the ability to copy records to accelerate data entry

Example of a Screen Shot of a LIMS Stability Module- Formula Builder



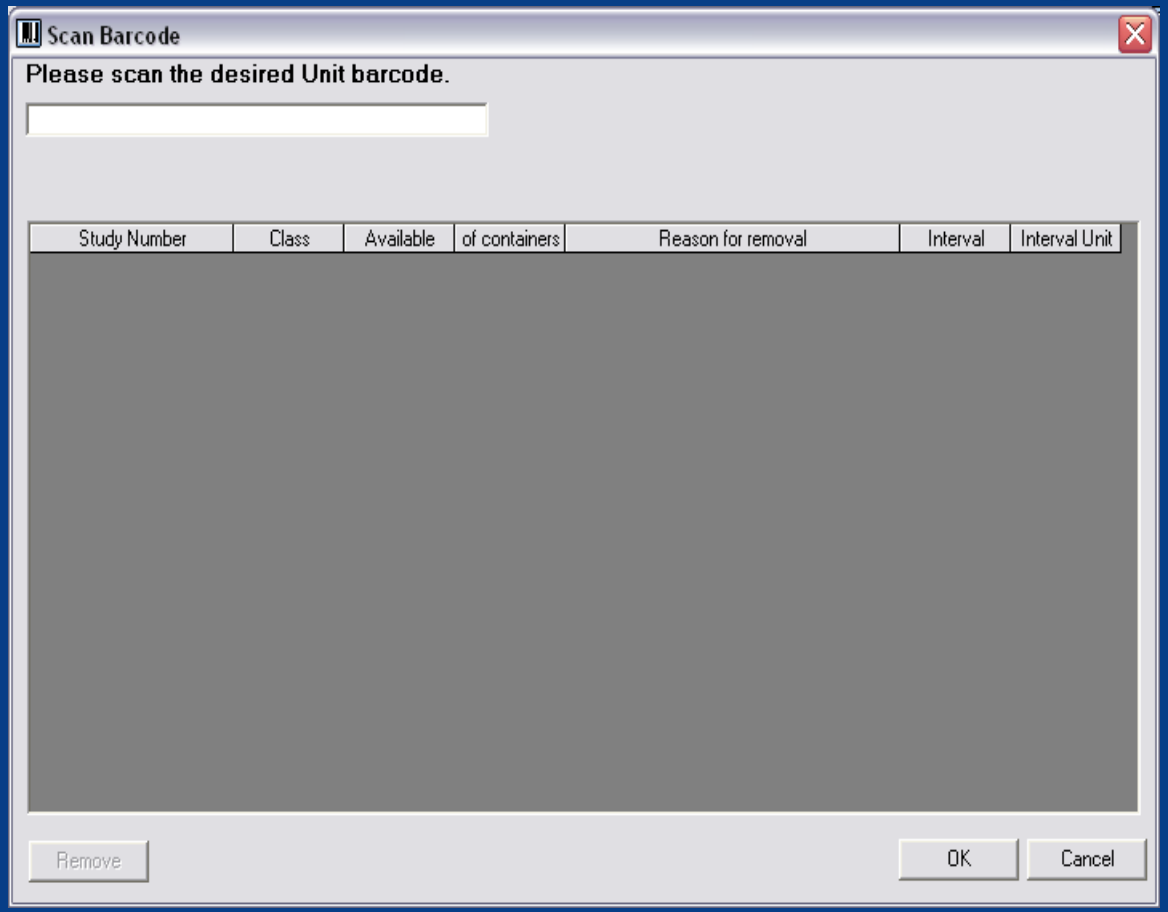
1. Creates and validates formulas
2. Has variable linkage across tests

Example of a Screen Shot of a LIMS Stability Module- Select Inventory



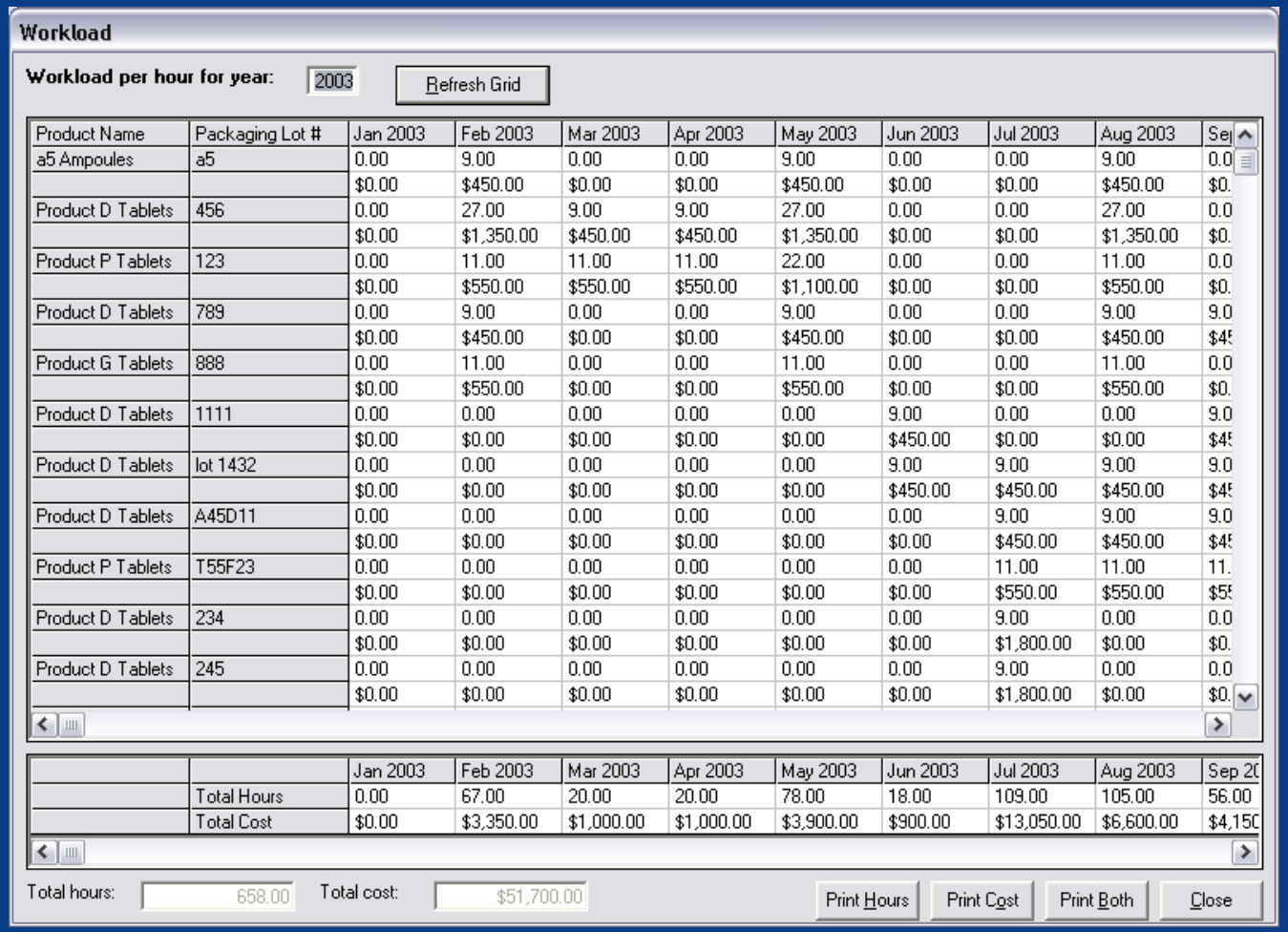
1. Keeps track of sample location by product and storage location
2. Allows for cancellation of some tests at any given interval.
3. Matrixing occurs here

Example of a Screen Shot of a LIMS Stability Module - Bar Coding



1. Generates labels for all samples automatically
2. Has sample tracking features which allows the facilitation of a rapid data entry process
3. Allows the pulling of test samples and navigation.

Example of a Screen Shot of a LIMS Stability Test Module -Workload



Workload

Workload per hour for year: 2003 Refresh Grid

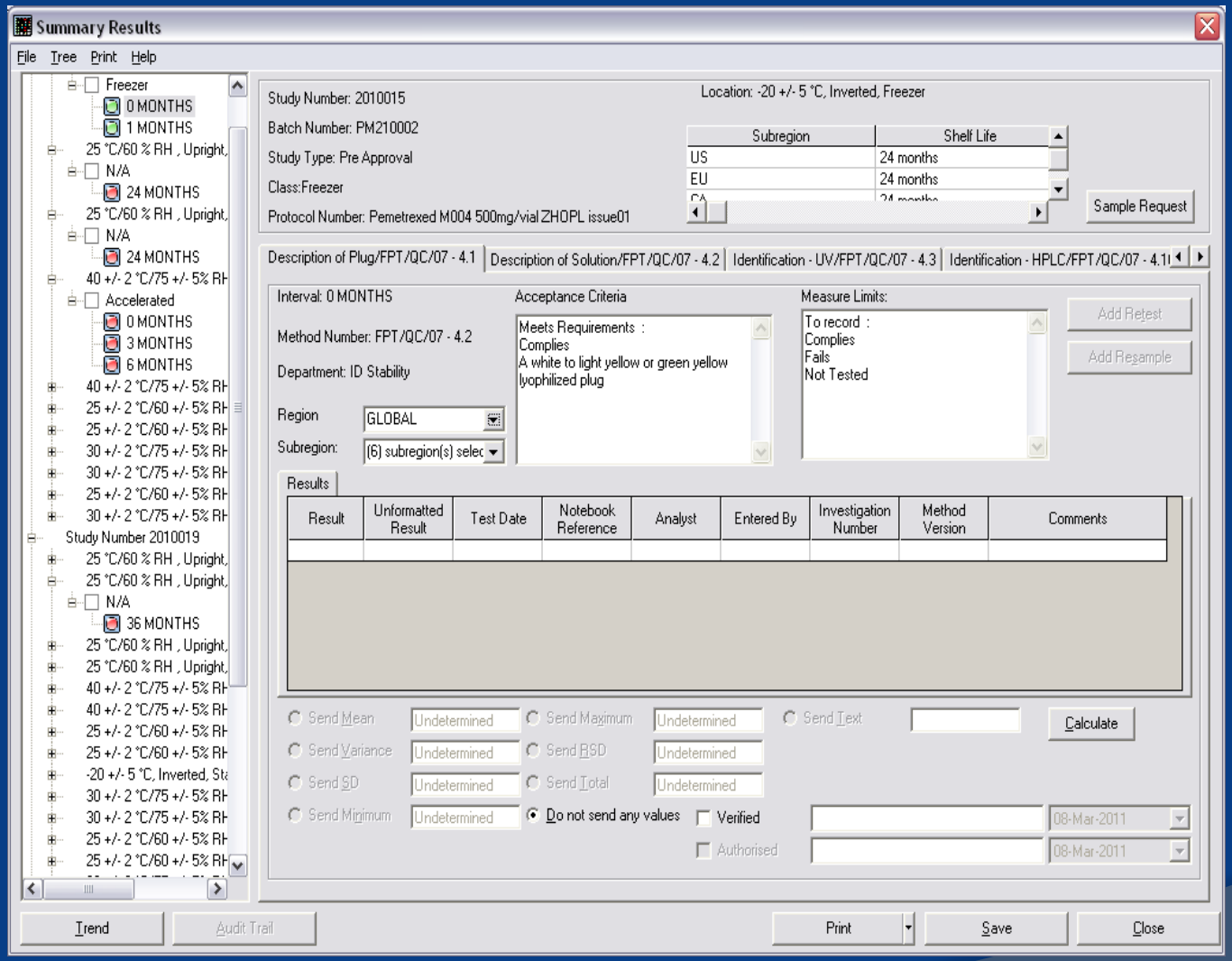
Product Name	Packaging Lot #	Jan 2003	Feb 2003	Mar 2003	Apr 2003	May 2003	Jun 2003	Jul 2003	Aug 2003	Sep
a5 Ampoules	a5	0.00	9.00	0.00	0.00	9.00	0.00	0.00	9.00	0.0
		$0.00	$450.00	$0.00	$0.00	$450.00	$0.00	$0.00	$450.00	$0.
Product D Tablets	456	0.00	27.00	9.00	9.00	27.00	0.00	0.00	27.00	0.0
		$0.00	$1,350.00	$450.00	$450.00	$1,350.00	$0.00	$0.00	$1,350.00	$0.
Product P Tablets	123	0.00	11.00	11.00	11.00	22.00	0.00	0.00	11.00	0.0
		$0.00	$550.00	$550.00	$550.00	$1,100.00	$0.00	$0.00	$550.00	$0.
Product D Tablets	789	0.00	9.00	0.00	0.00	9.00	0.00	0.00	9.00	9.0
		$0.00	$450.00	$0.00	$0.00	$450.00	$0.00	$0.00	$450.00	$4
Product G Tablets	888	0.00	11.00	0.00	0.00	11.00	0.00	0.00	11.00	0.0
		$0.00	$550.00	$0.00	$0.00	$550.00	$0.00	$0.00	$550.00	$0.
Product D Tablets	1111	0.00	0.00	0.00	0.00	0.00	9.00	0.00	0.00	9.0
		$0.00	$0.00	$0.00	$0.00	$0.00	$450.00	$0.00	$0.00	$4
Product D Tablets	lot 1432	0.00	0.00	0.00	0.00	0.00	9.00	9.00	9.00	9.0
		$0.00	$0.00	$0.00	$0.00	$0.00	$450.00	$450.00	$450.00	$4
Product D Tablets	A45D11	0.00	0.00	0.00	0.00	0.00	0.00	9.00	9.00	9.0
		$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$450.00	$450.00	$4
Product P Tablets	T55F23	0.00	0.00	0.00	0.00	0.00	0.00	11.00	11.00	11.
		$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$550.00	$550.00	$5
Product D Tablets	234	0.00	0.00	0.00	0.00	0.00	0.00	9.00	0.00	0.0
		$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$1,800.00	$0.00	$0.
Product D Tablets	245	0.00	0.00	0.00	0.00	0.00	0.00	9.00	0.00	0.0
		$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$1,800.00	$0.00	$0.

		Jan 2003	Feb 2003	Mar 2003	Apr 2003	May 2003	Jun 2003	Jul 2003	Aug 2003	Sep 2(
	Total Hours	0.00	67.00	20.00	20.00	78.00	18.00	109.00	105.00	56.00
	Total Cost	$0.00	$3,350.00	$1,000.00	$1,000.00	$3,900.00	$900.00	$13,050.00	$6,600.00	$4,15(

Total hours: 658.00 Total cost: $51,700.00 Print Hours Print Cost Print Both Close

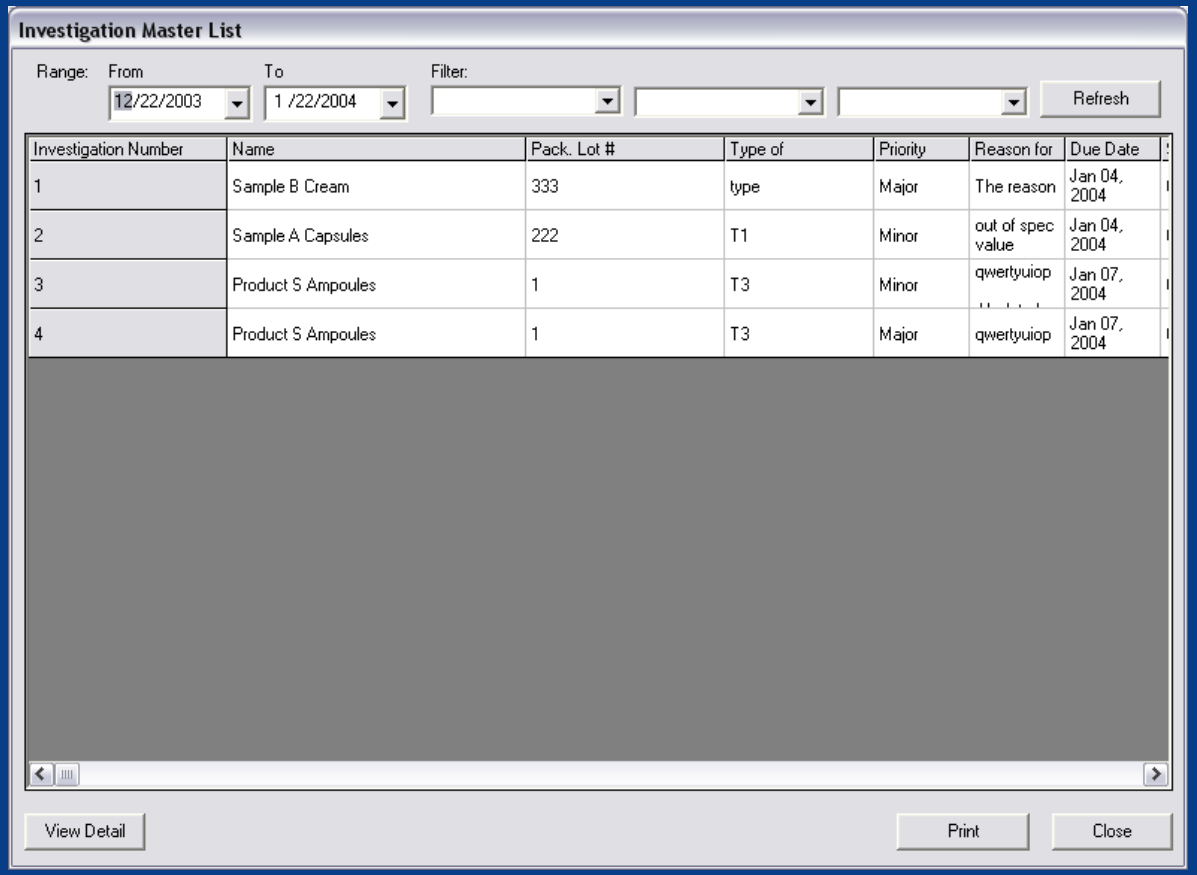
1. Has a tool for resource planning
2. Enables the user to forecast costs for a given time frame per stability study

Example of a Screen Shot of a LIMS Stability Test Module- Summary Window



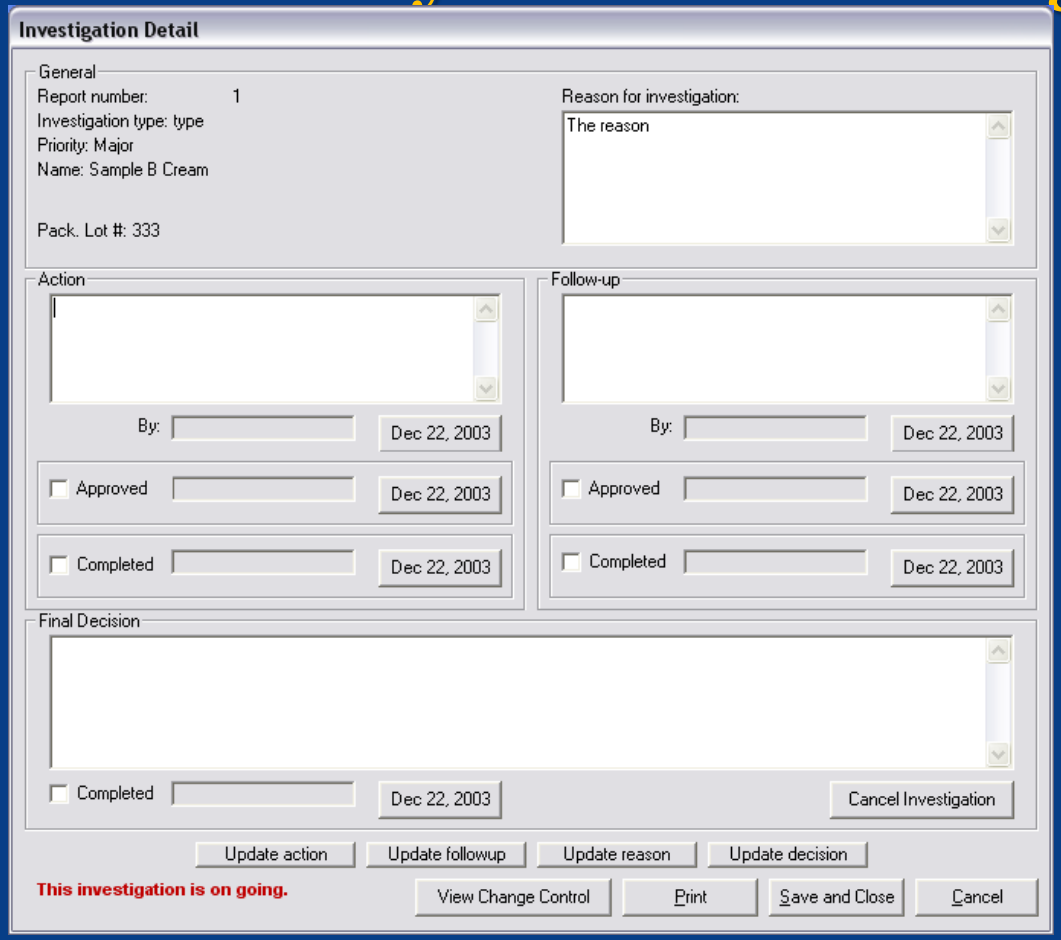
1. Allow for entry of results
2. Provides a summary of the parameters
3. Highlight out-of-specification results
4. Easy of Navigation between studies

Example of a Screen Shot of a LIMS Stability Module- Investigation Master List



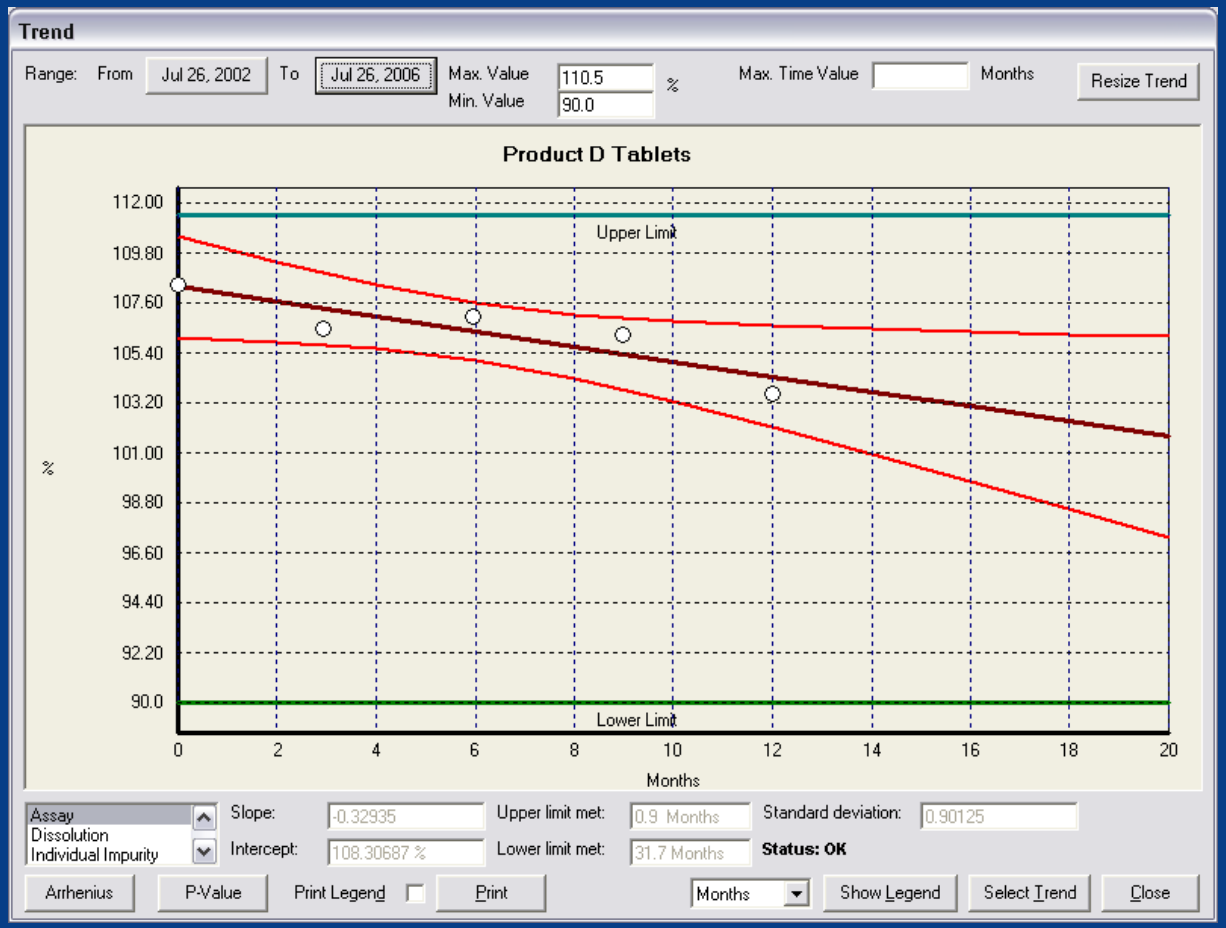
1. Each investigation should be assigned a unique number
2. Investigations should be filterable by date, product name, etc.

Example of a Screen Shot of a LIMS Stability Module-Investigation Details



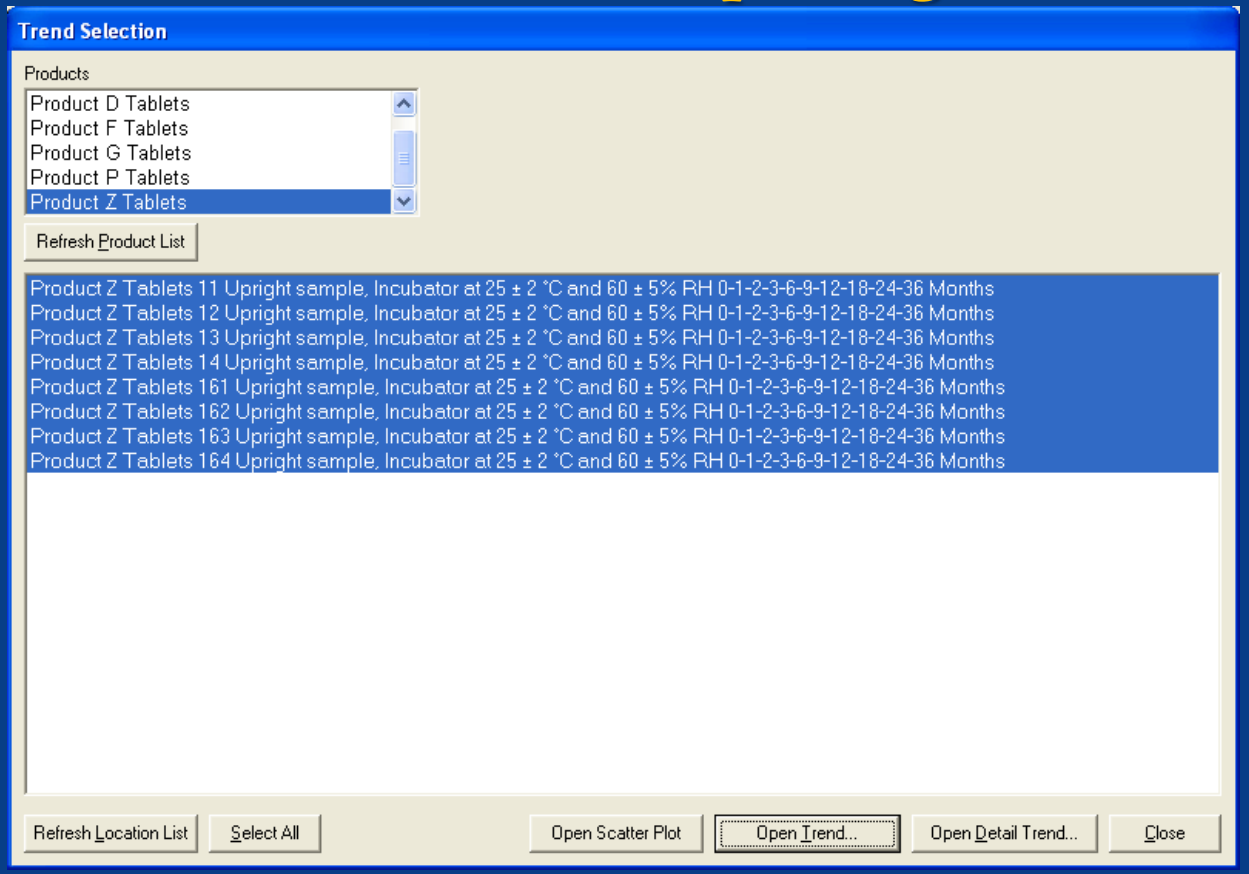
1. Allows for detailed OOS test result investigation
2. Can be linked to an existing CAPA investigation system
3. Includes a comment field for reason, action taken, follow up and final decision
4. Includes a three-step approval process

Example of a Screen Shot of a LIMS Stability Module- Statistical Analysis- Confidence Level Determination



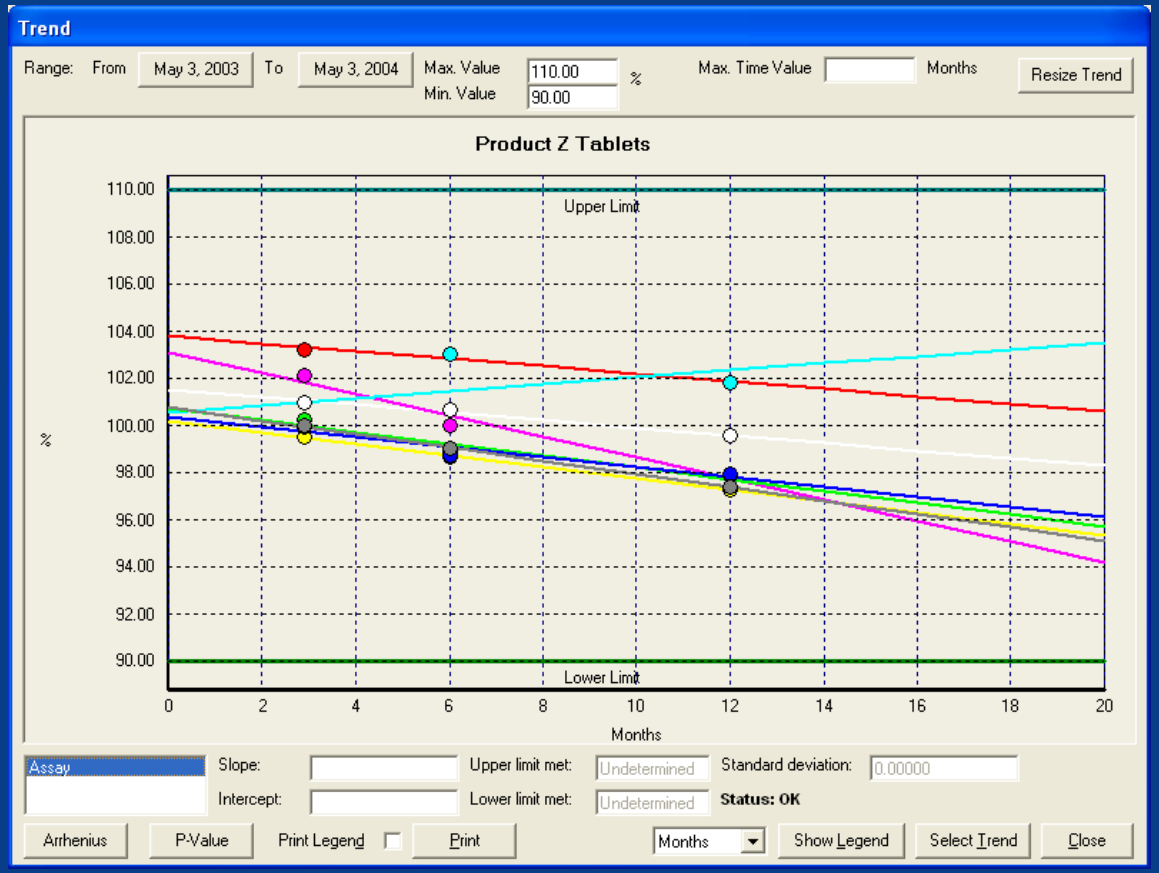
1. Should be able to trend by, study.
2. Specification levels
3. Upper and lower confidence levels
4. Regression line
5. Time points

Example of a Screen Shot of a LIMS Stability Module- Multiple Regression



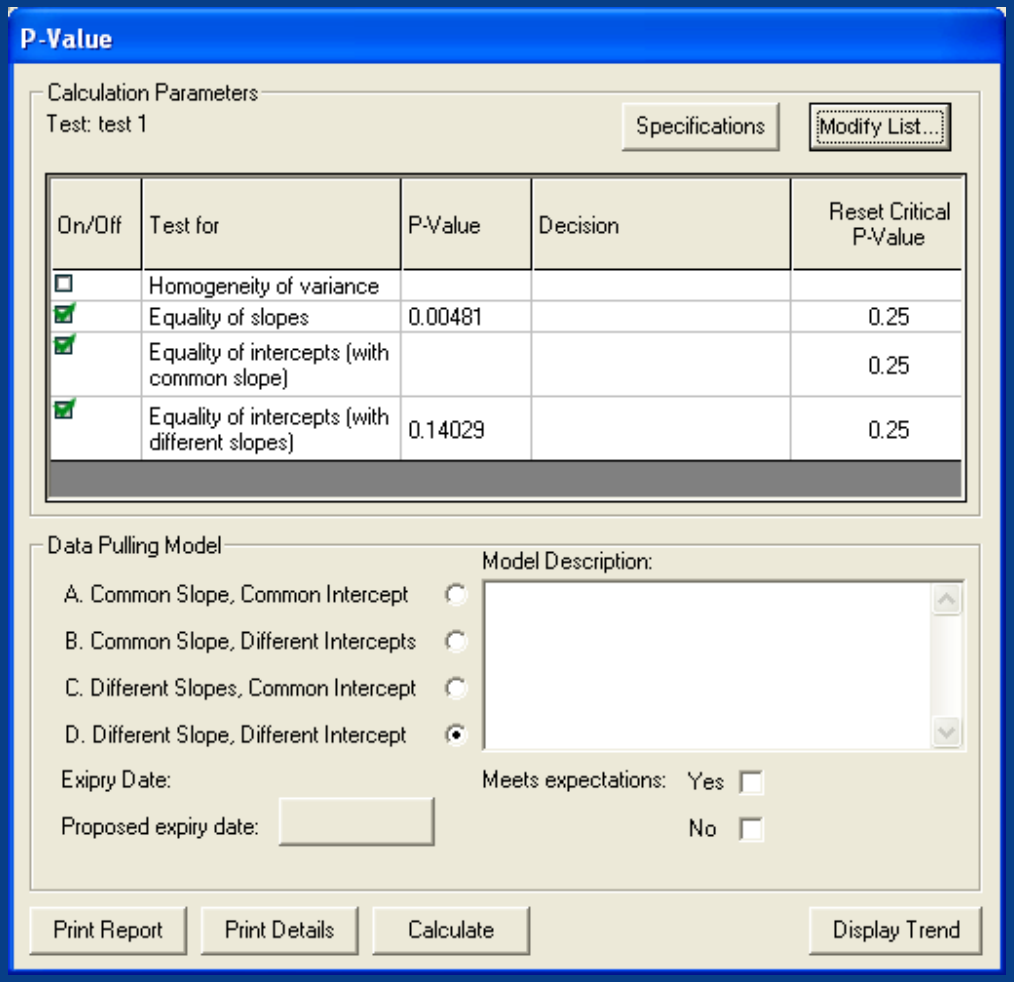
1. Select multiple studies
2. Select multiple locations
3. Trend separately
4. Trend together

Example of a Screen Shot of a LIMS Stability Module-Graphical Trend Using a Multiple Regression



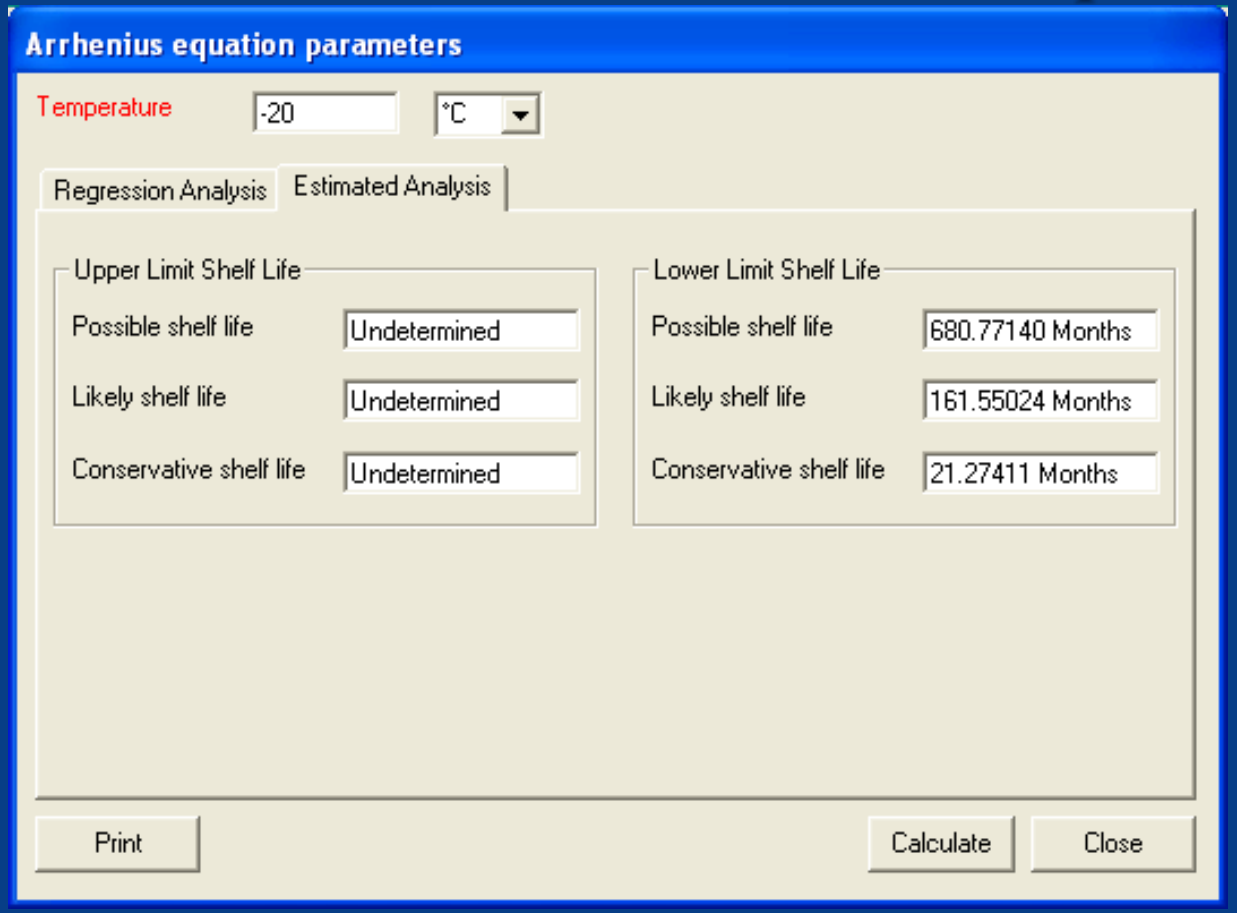
1. The x-axis and y-axis can be manipulated
2. A desired time value can be set
3. The Upper and lower limits can be checked to see if any was met

Example of a Screen Shot of a LIMS Stability Module-P-Value Calculations



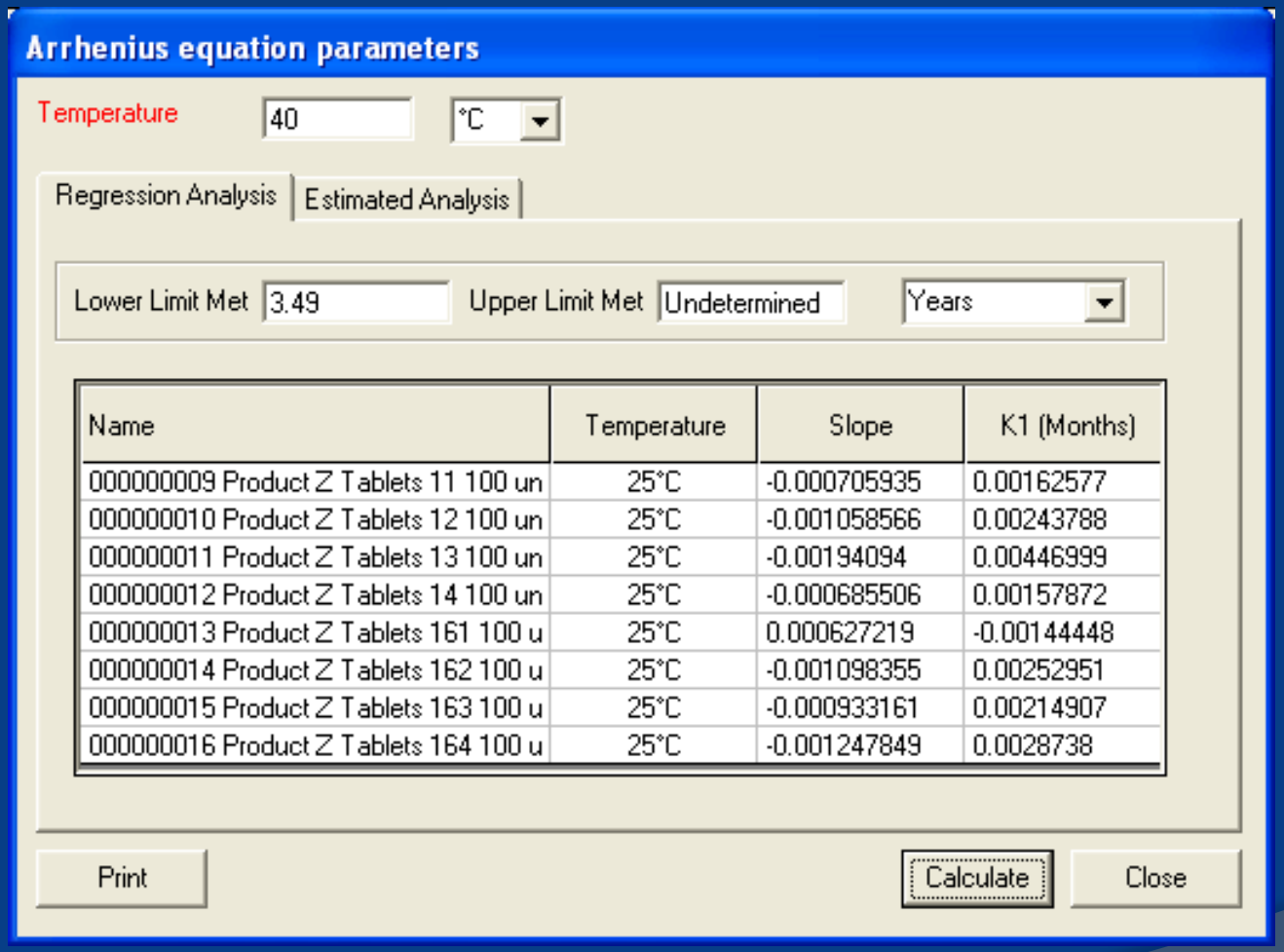
1. Calculate with different critical values.
2. Proper data pooling
3. Validated statistical package

Example of a Screen Shot of a LIMS Stability Module-Arrhenius Equation



1. When a single study is selected, the estimated Q10 method is used for calculation.

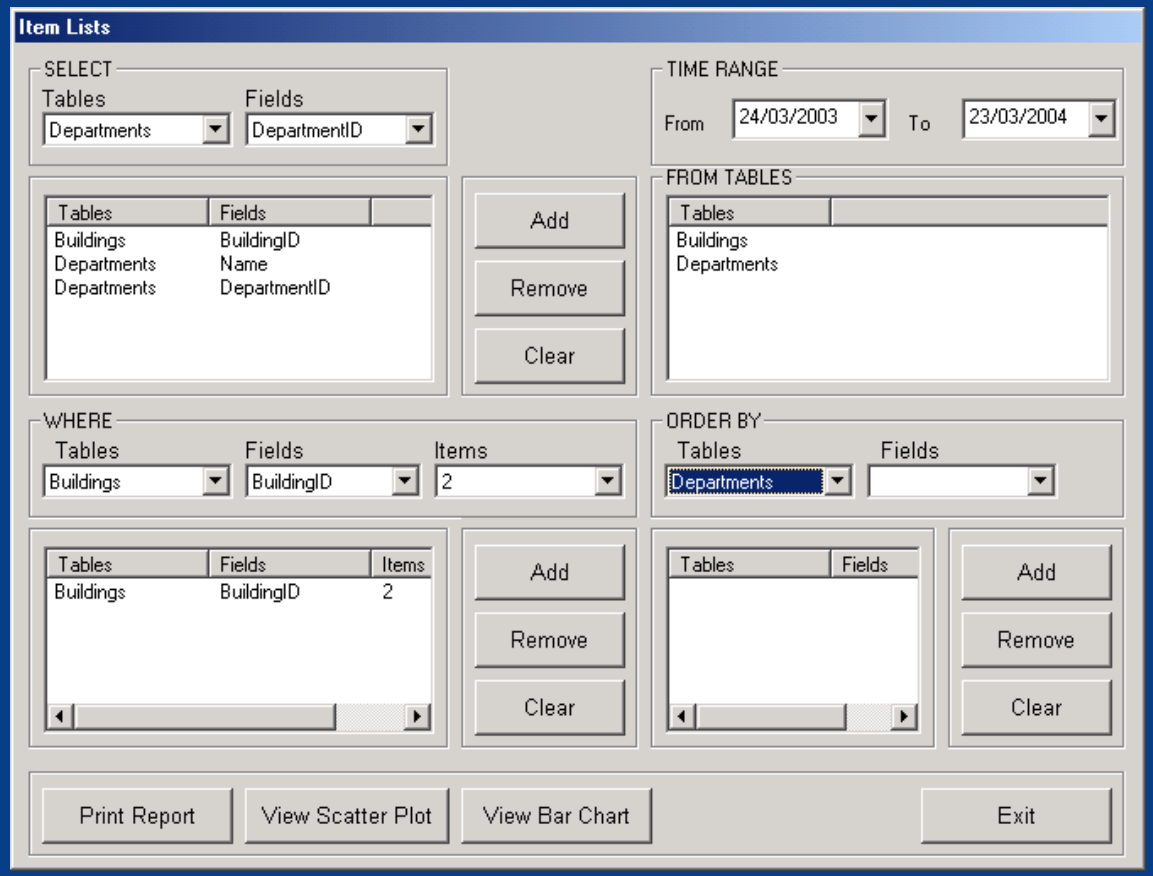
Example of a Screen Shot of a LIMS Stability Module-Arrhenius Equation



Name	Temperature	Slope	K1 (Months)
000000009 Product Z Tablets 11 100 un	25°C	-0.000705935	0.00162577
000000010 Product Z Tablets 12 100 un	25°C	-0.001058566	0.00243788
000000011 Product Z Tablets 13 100 un	25°C	-0.00194094	0.00446999
000000012 Product Z Tablets 14 100 un	25°C	-0.000685506	0.00157872
000000013 Product Z Tablets 161 100 u	25°C	0.000627219	-0.00144448
000000014 Product Z Tablets 162 100 u	25°C	-0.001098355	0.00252951
000000015 Product Z Tablets 163 100 u	25°C	-0.000933161	0.00214907
000000016 Product Z Tablets 164 100 u	25°C	-0.001247849	0.0028738

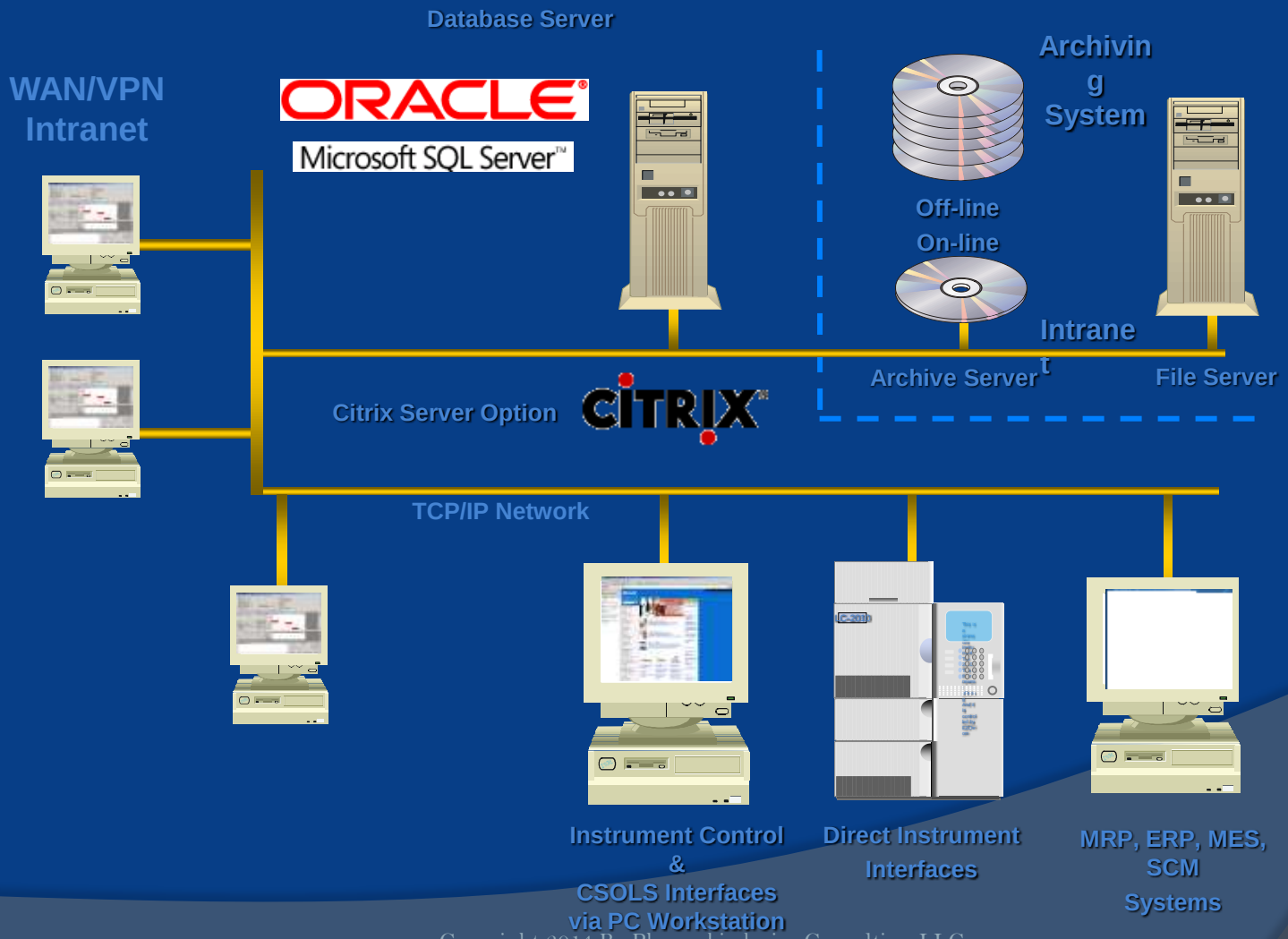
1. When multiple studies are selected, the first rate degradation equations are used

Example of a Screen Shot of a LIMS Stability Module- Free Format Query



1. Manipulate the system data as is needed while remaining in a compliant state.
2. On-demand data retrieval
3. Complete data manipulation with click of a mouse.

LIMS System Architecture-Novatek LIMS System



2:30 a.m. – 2:45 p.m.

Break

2:45 p.m. – 3:45 p.m

Session 4

Key Discussion Topics

- ❑Considerations Performing Analytical and Quality Control Testing
- ❑Setting Test Specification and Assay Release Process in a Stability Testing Program.
- ❑Criticality between an Effective Analytical Assay Design and a Successful Product Shelf Life Determination.
- ❑Choice of Test Assay Methods (Stability Indicator)
- ❑Analytical Assay Test Method Qualification/Validation Attributes
- ❑Review of Case Studies

Session 4-Learning Objectives

- **Choosing Analytical Assays and Other Considerations**
  - Consideration when determining a specific analytical assay or Quality Control Testing.
  - Consideration when setting assay test specification.
  - Relationship between the choice of an assay test method and specification are key to successfully determining the shelf life of a product.
  - Choice of test assay or methods with meaningful data or provides information as stability indicating.
  - Impact of the test result to the product's shelf life or expiry date.

Session 4-Learning Objectives

- Product Stability Indicator Tests:
  - Potency as a key indicator test
  - Other indicator tests and their roles
- Performing a compliant sample analysis.
- Effecting the appropriate test specification for the specific test and product type.
- Key features of an analytical assay test method qualification and validation parameters and attributes
- Review of Three (3) Case Studies
  - Issues Encountered by Drug Product Manufacturers Based on a Poorly Designed Stability Testing Program

Analytical/Quality Control Testing Considerations

- **Initial Considerations for Analytical and Quality Control Test Methods**
  - Best to consider using analytical test methods as follows:
    - Test methods must be reliable, meaningful, and specific 21 CFR. 211.166 (a) (3) .
    - Provides meaningful and reliable test data and provides useful information about the functional aspects of the product.
    - That will be sufficiently specific to differentiate between the unaltered drug and any possible degradation products.
    - That is already qualified or validated (based on the phase of the product)
    - May be able to be qualified or validated (i.e. validated for accuracy and precision).
      - Analysis should be conducted in replicate (duplicate preferred)
      - Raw data must be reported appropriately.
    - Describe the test method in detail.

Impact of an Effectively Designed Analytical Assay and Product Shelf Life Determination

- A well designed and established analytical assay allows the following to occur:
  - Ease of use, qualification or validation of the assay.
  - Ease of setting a reliable test specification for the assay.
  - Eliminates future out of specification and failure results.
  - Provides an accurate test data used to evaluate the product profile.
  - The product profile provides the basis for the statistical evaluation and trending of the data for each time point.
  - The trend and statistical data provides a basis for the determination of the product shelf life or expiry.
  - In summary, a well designed assay is defendable, will maximize the potential of the product performance leading to an accurate shelf life prediction for the product.

Setting Analytical Assay Test Specification

- **Best Practices on Setting Analytical Test Specification**
  - Plan ahead and determine potential assay tests specification and range during the product development phase (if possible).
  - Evaluate potential assays to be used for stability testing program and determine the specification prior to the start of the program.
  - Quality specifications should is best based on calculations that involves biological variation.
    - Advantages is that they are directly related to medical needs.
  - Best practice to base test specification on ***"Biological Variation"***

Setting Analytical Assay Test Specification

- **Desirable Performance:** Defined by $CV_A < 0.50CV_I$ and the specifications generated is viewed as being generally applicable.
- **Optimum Performance:** Defined by $CV_A < 0.25CV_I$. The more stringent quality specifications generated by this formula may be used for quantities which the desirable performance standards **were easily achieved** with current technology and methodology
- **Minimum Performance**: Defined by $CV_A < 0.75CV_I$. The less stringent quality specifications generated using this formula may be used for quantities which the desirable performance standards **were not attainable** with current technology and methodology

CV = Coefficient of Variation

Analytical/Quality Control Test Method Considerations-Stability Indicating

- **Choice of Test - Stability Indicating**
  - Choice of test assay or methods with meaningful data or provides information as stability indicating. i.e. Potency as an example.
  - Data should prove method's suitability as stability-indicating for the product being tested.
  - USP, NF, AOAC, et. al. or other control methods may be used for assaying the finished products.

Analytical/Quality Control Test Method Considerations-Stability Indicating

- **Choice of Test - Stability Indicating**
  - All analytical test methods used to test selected stability attributes of drug products, drug substance or novel excipients must be shown to have adequate sensitivity, accuracy, precision and specificity for stability testing.
  - In-house quality control tests may be used.
  - Document all test results appropriately.

Considerations for Analytical/Quality Control Test Method Qualification Parameters

- Key features of an analytical assay test method qualification and validation parameters and attributes
  - Best to use a qualified or validated analytical methods (based on the product phase).
- Test method qualification or validation attributes should minimally include the following key attributes:
  - Accuracy
  - Precision
  - Limit of Detection
  - Specificity

Considerations for Analytical/Quality Control Test Method Qualification Parameters

- Complete Method Validation attributes includes the following attributes:
  - Accuracy
  - Precision
  - Specificity
  - Limit of Detection
  - Limit of Quantitation
  - Linearity and Range
  - Ruggedness
  - Robustness

Analytical/Quality Control Test Method Qualification Parameters

- **Accuracy:**
  - A statistical measurement of the difference between the average test results and true value when the latter is known.
  - Measured using the % recovery from spiked samples containing a known amount of drug.
- **Precision**
  - Repeatability of the method. Measured by the SD or Coefficient of variation of the method at the levels of interest

Analytical/Quality Control Test Method Qualification Parameters

- **Specificity**
  - Ability of the method to determine the active ingredient(s) as the intact molecule in the presence of other substances that could reasonably be expected to mask or simulate the analytical behavior of the active ingredient.
- **Limit of Detection**
  - The method must be able to respond to the least amount of the chemical under analysis.
  - This is the concentration that represents the smallest measure of an analyte that can be detected with reasonable certainty by a given analytical procedure

Review of Case Study #1

- Failure to have a written testing program designed to assess the stability characteristics of drug products in order to determine appropriate storage conditions and expirations dates [21 C.F.R. § 211.166(a)].

Review of Case Studies

- FDA's 483 observations and warning letters are common in this area.
- Approximately 11% of warning letters are associated with stability testing. Examples are as follows:
  - There is no adequate testing program that can assess the essential stability features of drugs.
  - There is no appropriate storage conditions.
  - There is appropriate expiration date calculation.
  - Stability testing could not determine the expiration date on the label claim on the drug products.
  - Some manufacturers do not simply have any stability testing period (schedule)for their product.

Review of Case Study #1

- Failure to have a written testing program designed to assess the stability characteristics of drug products in order to determine appropriate storage conditions and expirations dates [21 C.F.R. § 211.166(a)].

Review of Case Study #2

- Failure to have thoroughly investigated any unexplained discrepancy or the failure of a batch or any of its components to meet its specifications whether or not the batch has already been distributed [21 C.F.R. § 211.192].

Review of Case Study #3

- Failure to ensure your container closure system provided adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the drug product [21 C.F.R. § 211.94(b)].

Review of Case Study #4

- Failure to provide data to support expiration date. (9/7/12)
- Lack of reliable stability data to support expiration date. (9/30/12)
- Lack of data to support expiration date. Stability study not completed to support expiration date. (3/9/12)
- Failure to determine expiration dates for the distributed products. Failure to follow procedure to perform stability tests at a certain time and condition. Lack of assurance that drug product is stable throughout expiry.

Review of Case Study #5

- Failure to conduct supportive stability studies prior to release (9/30/12).
- Lack of stability testing to support expiration period. (4/27/12)
- No testing performed at 12 and 18 month time points to establish a shelf life of 30 months. (7/12/12)

Review of Case Study #6

- Inadequate evaluation of Out of Specification OOS results for 12 month stability samples. (8/29/11)
- Failure to conduct timely, adequate OOS investigation for assay during stability testing at 24 months stability time point. (4/24/12)
  - Retesting performed and average of the two set of results documented as passing results.
  - No root cause was determined, unable to invalidate initial OOS result.
  - Inadequate conclusion.
  - Investigation not extended to other lots associated with specific failure.
  - Failure to conduct a review of production operations.

3:45 p.m. – 4:00 p.m.

Questions!

Open Comments and Adjournment!

Thank You for Attending!