1.0 Purpose

The purpose of this SOP is to define the stability program requirements, including but not limited to the process for determining which batches are to be placed on stability, bracketing, matrixing, test selection, sample storage conditions, generation of stability protocols and reports, and general program organization. Stability testing is to provide evidence on how the quality and/or safety of a product vary with time under the influence of a variety of environmental factors, such as temperature, humidity, and light.

2.0 Scope

This procedure applies to all finished products manufactured at Ion Labs.

3.0 Responsibility

3.1 It is the responsibility of DC to maintain a stability batch list which includes tracking formulation changes and bottling configurations.

3.2 Quality is responsible for generating customer quality agreements or reviewing/approving customer supplied agreements.

3.3 It is the responsibility of QC Laboratory Personnel to maintain official copies of all stability program forms, and product files, determine when a stability protocol is required, select bracketing and matrixing options, test selection, and to generate stability protocols in the stability program software. The QC Laboratory is also responsible for performing stability testing and documenting the results, generating final reports (if applicable) upon the completion of stability testing for a batch, and maintaining a supported expiration interval log.

3.4 R&D is responsible for initiating accelerated stability studies to determine formula stability metrics. QC Lab personnel may govern the stability study and ensure samples are pulled and submitted to the laboratory for testing.

4.0 Definitions

4.1 **Established Expiration Interval** – An expiration interval that Ion Labs has confirmed is supported by the execution of approved stability protocols for three batches.

4.2 **Expiration/Best By Date** – The date placed on a product container that indicates the time point prior to which a batch of product should remain within the established specifications if the product is stored under the conditions defined on the packaging.

4.3 **Existing Product** – Any product previously manufactured at Ion Labs Inc. with a current formula, manufacturing process, and container closure system.

4.4 **Expiration Interval** – The time period during which a product should remain within the established specifications when stored under the conditions defined on the packaging.

4.5 **New Product** – Any product not previously manufactured at Ion Labs, Inc.

4.6 **Product Profile** – A file that contains the product formulation, finished product testing, stability testing and exemptions.

4.7 **Test Cycle** – A specified number of months before the best-by-date during which stability testing will be performed to ensure continued compliance with established specifications.

4.8 **Test Interval** - A specified number of months between stability assessments. A Test Interval is a predetermined fraction of the Test Cycle.

4.9 **Bracketing** – The design of a stability study such that only samples on the extremes of certain design factors (e.g., strength, fill, flavoring, etc.) are tested at all time points as in a full design. The design assumes that the stability of any intermediate levels is represented by the stability of the extremes tested.

4.10 **Matrixing** - The design of a stability schedule such that a subset of the total number of possible tests for all factor combinations would be tested at a specified time point. At a subsequent time point, another subset of tests for all factor combinations would be tested. The design assumes that the stability of each subset of analytes tested represents the stability of all analytes at a given time point.

4.11 **Micro Control Solution Stability Software** – Software utilized by QC Laboratory Personnel to create and maintain stability protocols, stability testing data, and stability protocol trend cards.

4.12 **NLT** – Not Less Than

4.13 **FPTT** – Finished Product Test Ticket

4.14 **OOS** – Out of Specification

4.15 **OOT** – Out of Trend

4.16 **BPR** – Batch Production Record

4.17 **DC** – Document Control

4.18 **QA** – Quality Assurance

4.19 **QC** – Quality Control

5.0 References

5.1 C-201, SOP, Deviation and Investigation Procedure

5.2 C-502, SOP, Record Storage, Retention, and Destruction

5.3 D-105, SOP, Out of Specification and Out of Trend Investigation

5.4 D-404, SOP, Finished Product Reserve Samples

5.5 D-821, SOP, Dickson Data Logger and Dickson Secure

5.6 E-702, SOP, Finished Product Sampling Procedure

5.7 F-505, SOP, Environmental Monitoring Program

5.8 21CFR111, Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling, or Holding Operations or Dietary Supplements

6.0 Stability Guidelines

6.1 The stability test cycle at minimum must reflect the best-by-date or expiration date on the package. Stability testing can be extended to validate stability for periods exceeding the best-by-date or expiration date.

6.2 Stability testing required, stability exemptions, along with any matrixing or bracketing approach, will be pre-defined and justified in the product profile.

6.3 For a single formulation, all bottling configurations will be stability tested using at least one batch. Bracketing may be used if defined and justified in product profile.

6.3.1 If a formula is bottled with and without desiccant, preservative, or other stabilizer, each packaging combination requires full stability.

6.4 For each unique product formulation identified by the formula number matrixed with bottling configuration, the first three batches manufactured are subject to stability testing.

6.4.1 Each time a formula is modified, stability restarts per DC tracking. The modified formula will be bracketed with previously released modified formulations.

6.4.2 Coated and uncoated tablets with the same composition require separate stability studies and bracketing is not permitted.

6.4.3 Vegetable and gelatin capsules with the same fill composition require separate stability studies.

6.5 Formulas, formula changes, bottling configurations matrixed with eligible stability batches are tracked using an Excel spreadsheet which is maintained by DC.

6.6 Once the first three lots of any formulation has successfully met all acceptance criteria as defined in the stability protocol, one lot per year will then be placed into the stability program.

6.7 All dietary supplements bulk-shipped or labeled with a manufacture date are not subject to stability testing.

6.7.1 The customer can request stability testing be performed on bulk purchased product with a quality agreement in place providing the customer submits sufficient packaged finished product samples in the appropriate packaging configuration to the Ion Labs QC Laboratory for retains and testing.

6.8 Products made for sample purposes only and not intended for sale or distribution and Pilot batches may be used for stability purposes if the batches meet these criteria:

6.8.1 The batch contains all ingredients that the finished product will contain.

6.8.2 The batch is packaged in similar closure systems

6.9 For any customer modification to the default stability program, a quality agreement will be prepared by QA defining the responsibilities of Ion Labs, Inc.

6.10 New stability program structures and guidelines can be retroactively applied to active protocols providing appropriate justification is sighted in each affected protocol.

7.0 Minimum Time Interval Guidelines

The below table defines proposed testing intervals for stability evaluation, room temperature studies only. Other temperature/ humidity studies may be performed using different pull schedules. The product profile will be the official document that defines testing intervals but may reference this table when setting up the stability study.

Product Type	First year	Second Year	After 2nd Year
Pharmaceutical	Every 3 months, i.e. 3, 6, 9, 12 months	Every 6 months, i.e. 18, 24 months	Annually
Dietary Supplement	Every 6 months, i.e. 6, 12 months	Every 6 months, i.e. 18, 24 months	Annually
Cosmetic	Every 6 months, i.e. 6, 12 months	Every 6 months, i.e. 18, 24 months	Annually
Food	Every 6 months, i.e. 6, 12 months	Every 6 months, i.e. 18, 24 months	Annually
Pet	Every 6 months, i.e. 6, 12 months	Every 6 months, i.e. 18, 24 months	Annually

8.0 Generating a Stability Protocol

8.1 Stability protocols will be created using the Micro Control Stability software.

8.1.1 Enter all product information as applicable for each stability study.

8.1.2 Enter all testing required and each time point that product will be pulled for stability evaluation.

8.1.3 Once the protocol has been generated, a copy will be printed, reviewed for accuracy against the product profile, and approved electronically by QC Laboratory Management.

9.0 Generating a Stability Trend Card

9.1.1 At each time point, all results will be entered into the stability software.

9.1.2 The data will be entered, reviewed, and approved inside of the stability software using electronic signature. The person entering the data cannot approve their own entries. A second person will review and approve data entries.

9.1.2.1 Alternatively, manual signatures can be used.

10.0 Maintaining Stability Testing

10.1 Any updates made to a product profile may impact a current stability study. An evaluation should occur at time of product profile update to assess any possible impacts to the current stability studies.

10.2 If a product profile change is made that impacts the acceptable ranges of any stability testing, an assessment of the current stability studies should occur to determine applicability to those studies.

10.3 A newer method can replace an older method with QC Laboratory Management approval in the following circumstances:

10.3.1 The new method is equal or superior to the original method.

10.3.2 An outsourced method has been validated in-house.

10.3.3 Any method change should be reflected on a revised product profile.

10.4 A stability test that has a validated in-house method can be outsourced to a qualified third party lab with QC Laboratory Management approval. Reference SOP D-202 for Outsource Testing Procedure.

10.5 The Stability Program Lead or designee will collect all stability data and enter it into the Micro Control Solutions Stability Software.

10.6 Once all testing intervals in the stability protocol are complete, the Stability Program Lead will print off the final trend card from the Micro Control Stability software and circulate the completed study for final review.

11.0 Stability Protocol and Sample Handling

11.1 At the beginning of each month the Stability Program Lead or designee will identify all the active stability protocols for that month. The "pull" list should be printed each month and stored in a binder so that each stability pull can be recalled if necessary. All pulled samples should be verified against pull list each month prior to laboratory submission.

11.2 The stability samples will be identified and collected. The stability samples should be labeled with correct testing for the sample that was pulled and delivered to the QC Laboratory.

11.3 Testing must be completed within the following month of the stability pull. Testing periods can be extended with justification and QC Laboratory Management for up to 30 additional days. If testing is not completed within this timeframe then a deviation will be required to justify the late testing. The exception would be if a sample is under investigation. The investigative documentation will then govern the testing timeframe of the sample.

11.4 At the end of each month, the pull schedule will be compared to completed studies for that month to ensure all testing was completed. If all testing has not been completed, QC Laboratory Management will be notified immediately for reconciliation.

11.5 If an out of specification test result is obtained for any stability test, QC Laboratory Management will be notified immediately.

11.5.1 Any necessary OOS investigations will be documented in accordance with SOP D-105 Out-of-Specification Test Results Investigation.

11.6 The Stability Protocol, Stability Trend Cards, Out-of-Specification Reports, Deviations, Addendums, and all raw data that comprise the stability protocol will be maintained in the protocol binder by the QC Laboratory.

11.7 The protocol will remain open and will be maintained by the QC Laboratory until all stability testing intervals are complete.

12.0 Stability Sample Storage

12.1 The temperature and humidity conditions in the Stability Retain Room will be monitored and tracked with calibrated instruments as per F-505, Environmental Monitoring Program.

12.1.1 The temperature and humidity conditions will be at ambient conditions, approximately 15° - 30°C and 20 - 75% RH.

12.1.2 The temperature and relative humidity conditions are tracked using Dickson Data Loggers. Data is downloaded and processed periodically via protocol and according to D-821, Dickson Data Logger and Dicksonware Secure.

12.1.3 If the temperature or humidity data demonstrates that the conditions have gone outside of the specified range, an investigation may be conducted and documented as per SOP C-201 Deviation and Investigation Procedure.

12.1.3.1 The investigation will include, but not be limited to, an assessment of the impact on the ongoing stability studies and corrective actions.

12.2 An electronic log will be used to document product retained for stability testing. The log will reference the following: Batch Number, Product Name/Description, Container Closure System, and Logged By/Date. This log is maintained by DC.

13.0 Revision History

Revision	Date	Description of Changes	CCR #	By
0	05/06/10	New	-	-
1	02/11/11	Details added discussing nutritional supplements and ambient room temperature	-	-
2	08/08/11	Corrected typographical error in section reference in step 5.4.1	-	-
3	10/05/12	Revised entire program for compliance with current industry practices and regulatory expectations	-	-
4	10/09/13	Changed quantitative determination criteria for labile compounds, added quantitative determination criteria for non-labile materials, changed exemption source to product profile, removed bracketing, redefined stability protocol inclusion criteria, removed tracking log, replaced with finished product trend cards, reduced responsibilities of Sales down to identifying exceptions to stability program, added criteria for stable analytes, use of stability protocols from T=0 to be tracked for entire stability testing cycle.	13-822	B. Johns
5	04/23/14	Restructured SOP. Added bracketing and matrixing. Redefined test cycle criteria. Master stability list managed by DC. Use of exemptions in stability protocol to define bracketing, matrixing and exclusions. Expanded Protocol Type 1 and Protocol Type 2 definitions	14-0381	B. Johns
6	07/21/14	Added inventory requirements. Added form D-501-F2.	14-0593	S. Millar
7	01/05/16	Reworded for improved clarity. Expanded testing and specification options for international products. Adjusted stability criteria. Increased specification to 100% and added stability by container specification.	16-0018	N. Zhang
8	06/20/16	Title Change. Addition of cosmetic criteria. Removed F-501-F2 and transferred log requirements to be completed electronically.	16-0421	B. Johns
9	10/18/19	Title Change. Updated SOP to be more in line with current lab practices. Merged with SOP D-501.0 to cover all finished products manufactured at Ion Labs. Added stability software.	19-0763	J. Sassman