1.0 Purpose

The purpose of this procedure is to define the Product Qualification process that allows for a reduced testing plan, which includes a full, routine, or periodic testing regime of dietary supplement products manufactured at Ion Nutritional Labs manufacturing facilities, while still ensuring that the finished dietary supplement product meets all specifications for identity, purity, strength, composition, and impurity limits.

2.0 Scope

This procedure applies to all dietary supplement formulations, pet products, and foods produced by Ion Nutritional Labs. The Ion Nutritional Labs criteria for reduced testing can be superseded with a testing program provided by the customer.

3.0 Responsibility

3.1 It is the responsibility of QC Chemists to test finished products for release and to confirm test results.

3.2 It is the responsibility of QC Laboratory Management and R&D to determine risk level to select which formulations are eligible for reduced testing.

3.3 QC and R&D Management will determine the testing schedule and generate tracking sheets which predefine the testing to include full, routine, and periodic.

3.4 It is the responsibility of QC and DC to maintain all required documentation in support of the reduced testing program.

3.5 It is the responsibility of DC to maintain copies of the product profiles with the reduced testing exemptions and eligibility exceptions for reduced testing.

4.0 Definitions

4.1 **QC** – Quality Control

4.2 **R&D** – Research and Development

4.3 **DC** – Document Control

4.4 **Certificate of Analysis (CofA)** – A formal laboratory-prepared document that details the results and analytical methods for one or more laboratory analyses

4.5 **Certificate of Compliance (CofC)** – A formal document which certifies that the goods supplied meet the required standards

4.6 **Full lot test –** a test of a lot for all product attributes that might occur that are not either a qualification or a requalification (i.e. annual, periodic, or formula change)

4.7 **TYPE 1 Stability** – to establish the expiration interval of a formulation or modified formula

4.8 **Qualification** – the process of testing all attributes of a lot when a product is first developed or modified or for a product's annual full test

4.9 **Requalification** – the process of verifying the qualification of a product after a confirmed variance in the product is observed. There may be a change in the product formulation to correct for the observed variance.

4.10 **Optimal Testing Frequency** – a calculation derived from the number of lots produced during a three year cycle (N) using the formula (square root of N + 1) to determine the number of lots that are not full tested before a lot is full tested again

4.11 **NFP** – Nutritional Facts Panel

4.12 **Rotation Schedule** – a product's testing rotation of active ingredients for each lot based on the optimal testing frequency calculations and other factors

4.13 **Minimum Quality Control (MQC)** – the minimum testing that must be conducted on each lot which accomplishes the most amount of reduction in attribute testing

4.14 **Full Testing** – all active ingredient tests including other testing parameters are conducted

4.15 **Reduced Testing** – all active ingredients are tested with other testing parameters but testing is divided over consecutive lots, with each lot being tested for a minimum of one active ingredient

4.16 **Routine Testing** – all active ingredients are tested with other testing parameters but testing schedule is divided over consecutive lots and every other lot gets tested at least one active ingredient test (minimum quality control testing applies to this test regime)

4.17 **Periodic Testing** – all active ingredients are tested with other testing parameters but some lots may not have any active ingredient tests depending on the calculated test frequency (minimum quality control testing applies)

4.18 **Skip Lot Testing** – all active ingredient tests are conducted over a subset of lots produced (minimum quality control testing does not apply) **Note**: This is not considered a reliable testing plan and will only be applied by customer request

5.0 References

5.1 21 CFR 111.75 - What must you do to determine whether specifications are met?

5.2 21 CFR 111 subpart M – Holding and Distributing

5.3 D-401, SOP, Finished Product Testing and Specification Requirements

5.4 D-902, SOP, Establishment of Specifications

5.5 ICH Q7 – Good Manufacturing Practices for Active Pharmaceutical Ingredients document

5.6 21 CFR 101.9 – Nutrition Labeling for Food

6.0 Procedure

6.1 Product Qualification:

6.1.1 Products manufactured in-house at Ion Nutritional Labs facilities will be qualified by verifying that using a specific set of raw materials evaluated in accordance to the Raw Material Testing Summary, warehouse controls, a master formula, master batch record, manufacturing controls, and quality management systems to ensure that the dietary supplement product consistently meets the established product specifications. The warehouse controls are set in place to comply with warehouse or other storage facilities holding a dietary supplement as described in subpart M in FDA 21 CFR 111. The requirements for release are that every finished batch of dietary supplement meets each product specification for identity, purity, strength, composition and limits on contamination that may adulterate a finished product produced at Ion Nutritional Labs as per 21 CFR 111.75.

6.1.2 Following best practices outlined by the ICH Q7 Good Manufacturing Practices for Active Pharmaceutical Ingredients document, the first three (3) qualification production lots of a product are fully evaluated for identity, purity, strength, composition and limits on potential contaminants per the Finished Product Test Ticket.

6.1.3 Specifications for the Nutritional Supplemental Facts as defined in 21 CFR 101.9, Nutrition Labeling of Food, which includes calorie, total fat, cholesterol, total carbohydrates, fiber and sugars will be established based on calculation and then evaluated as report only on the first production lot of the product as a part of the product qualification.

6.1.4 The minimum required identification testing includes organoleptic analysis, macroscopic analysis and at least one chemical analysis or other scientifically valid method to definitively identify the material. Identification is considered a Minimum Quality Control (MQC) parameter and will be tested on every single lot regardless of testing program established for release.

6.1.5 The minimum required purity testing includes Microbiological Purity specified for the product unless the product has been placed on an alternate testing schedule. Justification for routine or periodic testing is based on risk assessment using historical analysis, biocidal status, and other factors that may impact microbiological purity of the product.

6.1.6 The minimum required physical parameter QC laboratory testing includes unit average weight, weight variation, density, pH, viscosity, total dissolved solids, and other physical parameters are examined as specified for the product. All physical property parameters are considered MQC and will be tested on every lot unless otherwise specified by the customer.

6.1.7 Following the successful completion of the qualification lots, a full, routine, or periodic testing schedule may be employed for all parameters not covered under MQC.

6.1.8 Unless otherwise specified by the customer, product contamination testing which may include elemental impurities, pesticides, residual solvents, melamine, gluten, peroxide value, acid value, various toxins will be reduced to an annual evaluation provided the data from the product qualification support the reduced testing practice. Vendor incoming raw material CofA's should be screened routinely for contaminant limits to ensure the materials are suitable for use in manufacturing.

6.1.8.1 In instances where the product is shipped to a region or country where certain contaminants are tested on every lot, the Finish Product Test Ticket will define the periodicity of the contaminant testing.

6.2 Routine Rotational Testing:

6.2.1 A routine rotational schedule begins after three (3) lots are fully tested. A risk assessment is performed after the three lots are completed to confirm the product is eligible. Confirmed failures of any specified test, reformulation during the test period and other changes or confirmations can lead a product being ineligible for a routine rotational schedule until additional data is collected to confirm the robustness of the formula and manufacturing process. This type of rotational testing can be selected by the customer.

6.2.2 The testing frequency for a routine rotational schedule can vary between less than full testing and testing a subset of ingredients in a rotation. Testing frequency can be customer defined with consideration of the product risk.

6.2.3 The testing for successive lots will rotate through the subsets of active ingredients sequentially until all active ingredients tests have been completed before the rotational schedule repeats. The rotational selection is predefined and can only be changed by events such as a confirmed out of specification or a change in formulation, both of which require the requalification of the product.

6.2.4 A minimum of one annual full testing is required for each calendar year. A full testing cycle can be substituted for any rotation cycle in the routine rotational schedule at any time.

6.3 Periodic Rotational Testing:

6.3.1 A periodic rotational schedule begins after three (3) lots are fully tested. A risk assessment is performed after the three lots are completed to confirm the product is eligible. Confirmed failures of any specified test, reformulation

during the test period and other changes or confirmations can lead a product to being ineligible for a periodic rotational schedule until additional data is collected to confirm the robustness of the formula and manufacturing process. This type of rotational testing can be selected by the customer. If in house stability testing is performed, at least one eligible stability batch will have all analyzable markers tested when the markers are required as a part of a Type 1 Stability assessment.

6.3.2 The testing frequency for a periodic rotational schedule can vary between less than every other active ingredient to testing a subset of ingredients in a rotation with MQC only testing performed at different frequencies between each subset of ingredient testing. Testing frequency is defined considering product risk and can be customer defined. The periodic testing frequency is typically less than the routine rotational frequency.

6.3.3 The testing of successive lots will rotate through the subsets of active ingredients sequentially until all active ingredients tests have been completed before the rotational schedule repeats. The rotational selection is predefined and can only be changed by events such as a confirmed out of specification or a change in formulation, both of which requires the requalification of the product.

6.3.4 A minimum of one annual full testing is required for each calendar year. A full testing cycle can be substituted for any rotation cycle in the routine rotational schedule at any time.

6.4 Rotation Schedule Examples:

6.4.1 Table 1 provides an example of how the routine rotational schedule would proceed for a hypothetical product that has three active ingredients (AI) and is eligible for routine testing with a customer request of at least one label claim ingredient (LCI) tested every lot:

Table 1:

Lot# of Formula SCT00XXX	Testing required
1st 451230	Full Testing: all LCI, NFP and MQCs
2nd 451240	Full Testing: all LCI and MQCs
3rd 451250	Full Testing: all LCI and MQCs
4th 451260	Reduced testing: A1 with MQCs
5th 451270	Reduced testing: A2 with MQCs
6th 451280	Reduced testing: A3 with MQCs
7th 451290	Reduced testing: A1with MQCs
8th 451300	Reduced testing: A2 with MQCs

NFP = Nutritional facts panel. MQC = Minimum quality control

6.4.2 Table 2 provides an example of how the periodic rotational schedule would proceed for a hypothetical product that has three active ingredients (AI) and is eligible for periodic testing assuming the risk assessment with customer approval calls for a ratio of testing 1 lot, skip rotate 3 lots:

Table 2:

Lot# of Formula SCT000XXX	Testing required
1st 451230	Full Testing: all LCI, NFP and MQCs
2nd 451240	Full Testing: all LCI and MQCs
3rd 451250	Full Testing: all LCI and MQCs
4th 451260	Reduced testing: A1 with MQCs
5th 451270	Reduced testing: MQCs only
6th 451280	Reduced testing: MQCs only
7th 451290	Reduced testing: MQCs only
8th 451300	Reduced testing A2 with MQCs
9th 451310	Reduced testing: MQCs only
10th 451320	Reduced testing: MQCs only
11th 451330	Reduced testing: MQCs only
12th 451340	Reduced testing A3 with MQCs
13th 451350	Reduced testing: MQCs only
14th 451360	Reduced testing: MQCs only
15th 451370	Reduced testing: MQCs only
16th 451380 (Repeat cycle)	Reduced testing: A1 with MQCs

LCI = Label Claim Ingredients NFP = Nutritional facts panel. MQC = Minimum quality control

6.5 Full lot, Qualification and Requalification Testing:

6.5.1 A full lot test of the product which includes a complete evaluation for identity, purity, strength, composition and limits on potential contaminants as per the Finished Product Test Ticket is conducted.

6.5.1.1 Once annually for all products regardless of reduced testing program implemented.

6.5.1.2 Once every 20th lot with routine testing and once every 30th lot with periodic testing for all products with 100 production lots per year is the default requirement. Products with less than 100 production lots require only annual. Periodic full testing cycles can be defined by Optimal Test Frequency calculations and by customer requirement.

6.5.2 Qualification is performed when a new formula has started production. A complete evaluation for identity, purity, strength, composition and limits on potential contaminants as per the Finished Product Test Ticket is performed.

6.5.2.1 The first lot in the series for the qualification requires NFP testing if the label contains a nutritional facts panel.

6.5.3 Requalification includes a complete evaluation for identify, strength, purity, composition and limits on contaminants as per the Finished Product Test Ticket. Requalification is performed when:

6.5.3.1 A master formulation change has been made that involves an ingredient composition adjustment or a significant change to the manufacturing process. Requalification using full testing for a minimum of the first three lots is required.

6.5.3.2 A confirmed out of specification incident occurs due an unexplained variation or no determined root cause. A Material Review Board (MRB) review and disposition of the lot and corrective actions will be

performed to determine if requalification is required. A minimum of three lots are required to requalify a product.

6.5.3.3 Once annually as a best practice standard.

6.5.4 Exceptions where requalification is not required:

6.5.4.1 Out of Specification (OOS) result for a contaminant when it is not attributed to a manufacturing process that requires a significant change to eliminate the contamination risk.

6.5.4.2 OOS result where the root cause traces back to a raw material (RM) issue when correction of the RM issue eliminates the risk to the product.

6.5.4.3 A failure in an Ingredient Addition Verification (IAV) calculation that traces back to an RM or production issue when correction of the issue eliminates the risk to the product.

6.5.4.4 The decision to requalify must be reviewed and approved by Quality Control management and must align with customer requirements.

6.6 Documentation:

6.6.1 A tracking and data archiving system will be maintained which shows at minimum, the projection of the reduced testing cycle, the completed lots for testing, and which tests were performed, and the test results.

6.6.2 A reference to the master formulation under which the qualification was performed.

6.6.3 Identification of the minimum three or more lots used for the qualification.

6.6.4 Identification of lots used for requalification.

6.6.5 Identification of the annual requalification lot.

6.6.6 Electronic copies of the approved Finished Product Test Tickets for the lots evaluated for any level of qualification or requalification.

6.6.7 Maintain copies of OOS records evaluation of risk when implementing reduced testing.

6.6.8 Based on customer requirements, COAs and COCs can be generated as a part of the batch release to provide assurance that the product meets all quality and safety requirements.

7.0 Revision History

Revision	Date	Description of Changes	CCR #	By
0	02/08/16	New	15-1093	B. Johns
1	08/23/16	Add criteria for customer requested reduced testing. Added reduced testing requirements for liquids.	16-0758	B. Johns
2	12/02/19	3 year review. Minor clarification.	19-0912	J. Sassman
3	07/01/24	Complete rewrite of the program.	CC-24-0322	B. Johns