



A Summary of the Key Differences Between the FDA's Drug and Dietary Supplement GMPs (21 CFR Parts 211 vs. 111)

In general, the Part 111 GMP requirements, although similar, are less stringent and tend to be more flexible than the Part 211 GMP requirements. However, interestingly, in a few areas the Part 111 requirements are more explicit or detailed than Part 211, such as necessary documentation for equipment or instrument calibration [111.35(b)(3)] and material review/disposition [111.140(b)(3)].

Listed below are some of the key differences between the dietary supplement (Part 111) and pharmaceutical GMPs (Part 211).

Raw material testing: There is no requirement for the dietary supplement manufacturer to confirm the identity of non-dietary ingredients used in the finished dietary supplement product if the supplier has been previously qualified by the manufacturer [111.73(a)(2) vs 211.84(d)(1)].

Reserve samples: There is no requirement for the dietary supplement manufacturer to hold a reserve sample of each dietary ingredient. Only a reserve sample of each lot of the packaged and labeled finished dietary supplement is required [111.83(a) vs 211.170(a)].

Finished product testing: Dietary supplement manufacturers have the option of testing a subset of finished batches based on a sound statistical sampling plan or testing all finished product batches [111.75(c)]. They may also exempt one or more finished product specifications from verification prior to release of the batch for good cause and with appropriate documentation [11.75(d)]. Drug manufacturers are required to test each active pharmaceutical ingredient in each finished drug product batch [211.165(a)].

Process validation: There is no requirement in Part 111 for dietary supplement manufacturers to formally validate their manufacturing process for each product.

Analytical method validation: Part 111 requires that dietary supplement manufacturers must identify and use appropriate, "scientifically valid" methods for each established specification [111.75(h)(1) and 111,320(b)]. In the Preamble to Part 111 (page 401) FDA gives some guidance on what should constitute the validation elements and identified them as accuracy, precision, and specificity. Thus, the validation of dietary supplement analytical methods is not as stringent (does not require as many validation elements) as FDA requires for pharmaceutical analytical methods.

Expiration dating and stability testing: There are no requirements for expiration, shelf life, or "best if used by" date and associated stability testing for dietary supplements in Part 111. The Preamble to Part 111 (pages 410-413) states that if you use an expiration date on a product you should have data to support that date and a written testing program to assess product stability characteristics. FDA declined to provide guidance on the requirements for a dietary supplement stability as compared to drug manufacturers that are required to have expiration dates and formalized ICH compliant stability programs for their products (211.166).

Change control: There is no specific mention of change control in Part 111. It is alluded to in 111.30(d) and 111.105(a). This is a major area of attention for pharmaceutical manufacturers and an FDA expectation.

Quality control personnel: Part 111 allows greater flexibility to use the same quality control employee for QC operations and other operational activities provided he/she is qualified to do so and the responsibilities are separate and distinct [111.12(b)]. The Part 111 regulations also do not require that a separate quality (quality assurance) unit be established, only that the personnel responsible for QC operations are identified [11.12(b)]. This portion of the Part 111 regulations is intended to provide flexibility for small dietary supplement manufacturers who have limited staff.

Percentage of labeled amounts of ingredients: FDA requires that dietary supplement manufacturers ensure that each of the labeled dietary ingredients are present at 100% of the declared amounts throughout the expiration period of the product (*Federal Register* 62, page 49826, September 23, 1997), while pharmaceutical products must contain the declared amounts of the active ingredients within the pre-established specification ranges (e.g. assay 90-110%).

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