



White Paper

## New Dietary Supplement GMPs – Feast or Famine?

New Good Manufacturing Practices (GMP) for dietary supplements comes into force on 25<sup>th</sup> June 2008. This white paper highlights some of the key requirements that you will need to address in order to comply.

## Introduction

The US Food and Drug Administration (FDA) has released a new code of Good Manufacturing Practice (GMP) for dietary supplements - Chapter 21 of the Code of Federal Regulations part 111 (21 CFR part 111). The objective of 21 CFR part 111 is to ensure that dietary supplements are produced in a quality manner, do not contain contaminants or impurities, and are accurately labelled.

The new regulations became effective on 24<sup>th</sup> June 2007. Australian and New Zealand companies exporting dietary supplements for sale in the US must comply with the new requirements on or before the implementation dates detailed below. To allow smaller companies to modify their Quality Systems accordingly, a phased approach has been adopted.

Table 1: Implementation dates 21 CFR part 111.

Company Size (number of employees)	Compliance Date
500 or more	25-June-2008
20 or more but less than 500	25-June-2009
Less than 20	25 June-2010

Does this present an opportunity or threat to your company?

You will need to answer this for yourself, but history has shown that companies that react well to change are well placed to succeed.

## Why is the FDA Issuing a New Rule Specifically for Dietary Supplements?

The US FDA has an “umbrella” rule 21 CFR part 110 which defines the GMP requirements for food. The FDA defines food as a substance that provides nourishment to survive. The purpose of a dietary supplement however is to supplement ‘conventional’ food intake; not to act as the main source of nourishment for survival, therefore, a supplement is not a food and can’t be captured under 21 CFR part 110.

21 CFR part 111 also contains approximately 200 pages of preamble to further clarify why the FDA has implemented the new regulations.

## What does 21 CFR part 111 include?

This section highlights some of the key aspects of the new regulations:

### Written Procedures and Records

The new regulations apply pharmaceutical GMPs relating to written procedures and records. 21 CFR part 111 states that you should prepare written procedures for operations, and prepare master manufacturing records and batch records. You should also include pharmaceutical controls such as verification of ingredient addition and record yields (expressed as maximum and minimum values) for reconciliation purposes.

21 CFR part 111 also requires that specifications be established for all materials used during manufacture and that sampling plans are defined to assess ingredients against these specifications.

You won't find this level of control for food GMPs because dietary supplements are produced in dosage forms such as tablets, capsules, etc., and not 'serving' sizes.

## Personnel

Similar to the pharmaceutical GMPs, 21 CFR part 111 requires you to identify who is responsible for Quality Control activities. The responsible staff must have the appropriate education, training or experience to perform their duties. This also holds true for supervisory staff and those involved in manufacturing, packaging, or labelling product. 21 CFR part 111 allows you to define the level of education, training and experience necessary for each role, unlike other food GMPs (e.g. 21 CFR part 113 or 21 CFR part 114).

## Material Controls

21 CFR part 111 requires you to establish controls for received, in-process, and finished product materials including physical or logical segregation of materials that have and have not been released for use. This is based on the fundamental principles well established in pharmaceutical and medical device GMPs. Material control also relates directly to the design of the facility and its associated control systems.

As experienced GMP compliance consultants, PharmOut recognise this is a key area of interest to the FDA and other Regulatory Authorities during on-site audits.

## Product Testing

21 CFR part 111 is flexible about finished product testing. Rather than testing each batch, you can employ statistical sampling and testing programs; however, you need to fully understand the context in which the FDA permits this type of sampling. 21 CFR part 111 states that you can use statistical sampling and testing programs only when you have implemented controls earlier in the manufacturing process, such as quality control of the ingredients, or in-process manufacturing controls.

The new regulations also require you to retain samples of ingredients, in-process materials, packaging, labels, and finished product for one year past the shelf life of the finished product.

## Incident Management

21 CFR part 111 requires you to establish systems for adverse reporting and complaints. The aim is to identify quality related issues during batch manufacture and to have a system to implement corrective and preventive actions as required. In order to have an effective incident management system it is important that your Quality Management System is effective and that good records are kept.

## What doesn't 21 CFR part 111 include?

The new regulations do not specifically reference validation or auditing. There is instead a statement that requires you to “ensure equipment operates in accordance with its intended use”. You should also provide “documentation setting forth the basis for qualification of any supplier”. The new regulations also state that “you must verify that the laboratory examination and testing methodologies are appropriate for their intended use”.

The text within the preamble to 21 CFR part 111 provides some insight into the FDA's thinking on supplier qualification by using a supply chain scenario. Within this scenario, the person who is releasing the final product for sale has “an obligation to know what and how such activities are performed so that they can make decisions related to whether the packaged and labelled product conforms to specification and whether to approve and release the product for distribution”. So if your company packs product into its retail package to release for sale you are “obliged” to know that the precursory steps have been conducted in compliance with the new regulations. This

also holds true for a wholesaler whose function is to store and distribute released product to retail outlets.

You should also be aware that 21 CFR part 11 (Electronic Records: Electronic Signatures) is applicable to all FDA regulated industries, including dietary supplements. Within 21 CFR part 11 the term validation **is** used therefore you must validate your computerised systems which are implicated by GMP accordingly. The systems implicated by GMP are defined in 21 CFR part 111 and set the boundaries for your compliance with 21 CFR part 11. 21 CFR part 111 also defines further requirements for “back up” and establishing controls so that only authorised personnel can modify computerised systems.

All GMP codes are open to interpretation. Comments during the discussion phase of the new regulations highlighted that the language used by the FDA such as “adequate,” “appropriate” and “suitable” are vague. These terms continue to be used but the emphasis is placed on individual companies to develop systems that fulfill the new requirements without prescribing how it should be done. Having flexibility within the regulations can be both a blessing and a curse as you are unaware if your system is compliant or whether you are going “over-the-top”.

## What should you do?

You should review your current Quality Systems against the new regulations to determine whether there are any gaps or excessive controls in place. It is important that when interpreting the new regulations that a risk-based approach is followed whereby the control is commensurate with the level of risk for that particular operation/product. In addition, you must ensure that you document your rationale for control strategies, including a summary of the risk assessment performed.

As leading compliance experts within Australasia, PharmOut can significantly reduce this effort and allow you to focus on your everyday business operations of making and selling quality products.

## References

Regulation	Title
21 CFR part 11	Electronic Records; Electronic Signatures
21 CFR part 110	Current Good Manufacturing Practice in Manufacturing, Packing, or Holding Human Food
21 CFR part 111	Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements
21 CFR part 113	Thermally Processed Low-Acid Foods Packaged in Hermetically Sealed Containers
21 CFR part 114	Acidified Foods

## About PharmOut

PharmOut is a boutique consultancy to the Pharmaceutical, Medical Device, and Veterinary drug industries.

PharmOut specialises in GMP compliance, validation and continuous improvement consulting, and training.

Some of PharmOut's customers include –

*Abbott Australasia (Healthcare), AC Immune SA, Acrux Limited, Agronico Research Pty Ltd, Amcor Limited, APHS Pty Ltd, AstraZeneca, Ausonex Pty Ltd, Austin Nuclear Medicine and Centre for PET, Australasian Lubricant Manufacturing Co., Avexa Limited, BD - Australia / New Zealand, Bernafon Pty Ltd, BioMerieux Australia Pty Ltd, CathRx Ltd, Chemeq Limited, ClearStep Australia Pty Ltd, CSL Bioplasma, CSL Parkville, Emerson Process Management, Ensign Laboratories, Enterix Pty Ltd, Faulding FH & Co Limited, Fonterra Co-operative Group, GCL Ltd, Go Medical, GSK, Hospira Pty Ltd, House With No Steps, IDT - Institute of Drug Technology, IG Science Pty Ltd, Intellidesign, Invetech Pty Ltd, Mayne Pharma Ltd, MDI - Medical Developments International, Pall Australia, Peplin Operations Pty Ltd, Pharmatel Fresenius Kabi Pty Limited, Probe Analytical - Intertek Caleb Brett, PT. Sanbe Farma, Royal Brisbane Women's Hospital, Siemens Ltd, Supercare Pty Ltd.*

## How PharmOut can help

We offer a range of services to assist companies with their compliance programmes while maintaining operational efficiencies:

### **GMP Gap Analysis**

We can assess your current Quality Systems and identify potential compliance gaps and operational inefficiencies. We achieve this through indepth knowledge of the codes of GMP and practical experience in implementing workable solutions through a risk-based approach.

The advantage to companies is that precious internal resources are not diverted from core business activities and it alleviates the pressure to set the high compliance levels to avoid mis-interpretations of the GMP requirements.



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