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Creating SOPs Under the Final GMP Rule to Assure the Identity, Purity, Strength, and Composition of Your Product

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Presentation Overview

- Compliance: Who?
- Strategies for melding GMPs into SOPs
- Strategies for product testing
- Maintaining value while implementing
- Monitoring remote operations
- Effects of GMP-compliance on supply chain

21 CFR 111 72 FR 34751 - 34958

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Read the Federal Register – Then Write SOPs

- 72 FR 34751 – 34958
  - p. 34761 Overview (FDA intent)
  - p. 34764 Highlights (requirements)
  - p. 34789 Comments & Responses
  - p. 34915 Paperwork (expectations?)
  - p. 34932 Costs (expectations?)
  - p. 34942 List of (Final) Subjects
  - p. 34943 The (Actual) Rules

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Compliance: Who?

- "If you manufacture, package, label, or hold a dietary supplement…"
  - Definition from Bioterrorism Act
- Applies to:
  - all domestic and foreign companies.
- Does not apply to:
  - companies that only manufacture or hold dietary ingredients.
  - companies only involved in harvesting, distribution or storage of agricultural commodities for incorporation into dietary supplements.
  - retailers that hold supplements for direct to consumers sales.

21 CFR Subpart A § 111.1

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Melding GMP into SOPs – Step 1

- Master the GMP Definitions

  Watch for nuances, contrasts, connotations

component	→	maintain *lot* control (packaging items, too)
contact surface	→	know when to *sanitize*

72 FR 34794 | 72 FR 34943

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Melding GMP into SOPs

- SOPs are required for
  - Subparts B thru D
  - Subparts F, G
  - Subparts J thru O
- SOPs not required
  - Subparts E, H, I, P

72 FR 34774

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Melding GMP into SOPs

- SOP Documents
  - If electronic, must comply → 21 CFR 11
  - Written records are acceptable!
  - There must be Document Control
  - There must be Change Control
  - QC must authorize SOPs, approve tests

"must" v "shall" must = a requirement
"includes" = "includes, but is not limited to"

72 FR 34797 | 72 FR 34765

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Testing & Quality Control

Example: Any qualified and/or experienced person not involved with or responsible for a given operation, can be trained and assigned to Quality. 21 CFR 111.12

Example: If a dietary ingredient is of land-based plant origin, "it is not likely you would include a limit on cadmium because cadmium is not a common contaminant of land-based plants."

72 FR 34837 | 72 FR 34800 (Quality Control def'n)

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Testing & Quality Control

- Acceptable Test Methods

  (used properly and consistently)

For ID:

Compendial Methods (USP, AOAC, FCC, JP, BP, EU, etc.), TLC, IR, HPLC, Mass Spec., ICP/MS, GC, HPLC, CE, Botanical ID, others

For Quantitative:

HPLC, GC, ICP/MS, CE, Compendia, others

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Testing Product In-Process

- Control Points (21 CFR 111.70)
  - "in process"
  - "any point, step, or stage"
  - "where control is necessary to help ensure that specifications are met"

- HACCP v CGMP (21 CFR 111.75)
  - HACCP: focus, anticipate, act to prevent
  - GMP: directs required prevention steps

72 FR 34949 | 72 FR 34846

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Testing Complex Formulas

- Use in-process assays to advantage
  - Graduated blending (multiple blends, additive per batch)

Micro-ingredient blends can be assayed prior to incorporation with other ingredients in a Batch. Then weight reconciliation can bring the assay into context for confirming identity, purity, strength and composition of the finished dosage.

72 FR 34949 | 21 CFR 111.75

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Optimizing $$ While Implementing

- Use what you already have: History
  - Reliable Master Formulas
  - Archived Batch Records
  - Retained Samples
  - Lab Records & Product Assays

Retrieve, Review, Analyze!

For writing unique Master Manufacturing records.

72 FR 34954 | 21 CFR Subparts H & I

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Optimizing Compliance Costs

- Inspect your processors
  - Ask for GMP compliance presentations
  - Have multiple contacts (know QC)
  - Look for independent 3rd party audits
  - Consider a consultant
  - Join a trade association

Ask everyone what they have to help you!

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Qualifying Components & Suppliers

- Questionnaires & Surveys (Instead of developing your own)
  - SIDI: Standardized Information on Dietary Ingredients

    (joint effort: NPA, CRN, CHPA, AHPA)

  - IPEC: International Pharmaceutical Excipients Council

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Monitoring Offsite Operations

- Be prepared for “routine” repetition of inspections, approvals, etc.

  every 1 – 2 years or more frequently.

- Set up systems that are efficient and questionnaires that can be returned easily. Weigh the burdens carefully.

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Effect of GMP-compliance on Supply Chain

- Tap suppliers for full value
  - Information
  - Lab support
  - Assay methods
  - Training and orientation
  - Support for QC issues

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Effect of GMP-compliance on Supply Chain

- Today's business environment
  - Tight supply on basics
    - Olympics & China
    - Lack of profitability
  - Increased costs
    - Raw materials
    - Energy & transportation
    - Ingredients of petrochemical origin
    - Food Supply v. Energy Supply

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Effect of GMP-compliance on Supply Chain

- Ultimately the entire supply chain will host higher quality standards in the face of competition.
- Consumers will gain confidence in Dietary Supplements made in the US.

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Lessons Learned

- Incorporate all the rules!
  - Do you need international compliances?
  - Include all US regulations – still required

FFD&C (NLEA, DSHEA)

FQPA (FIFRA)

Bioterrorism, FALCPA, NOP, AER, etc.

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GMP: Creating Sound SOPs

- ✓ Use what you already know (history)
- ✓ Everyone needs to know the GMPs
- ✓ Go for audits; use smart questionnaires
- ✓ Strive to be “consistent”
- ✓ Remember all the rules (not just GMP)
- ✓ Read the CFR & the Federal Register

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Assuring Key Aspects of Your Product

Identity

Purity

Strength

Composition

Quality is Engineered from the Start

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