

DDM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 111

Display Date 6-22-07  
Publication Date 6-25-07  
Certifier A. Corbin

[Docket No. 1996N-0417] (formerly Docket No. 96N-0417)

RIN 0910-AB88

**Current Good Manufacturing Practice in Manufacturing, Packaging,  
Labeling, or Holding Operations for Dietary Supplements**

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Final rule.

---

**SUMMARY:** The Food and Drug Administration (FDA) is issuing a final rule regarding current good manufacturing practice (CGMP) for dietary supplements. The final rule establishes the minimum CGMPs necessary for activities related to manufacturing, packaging, labeling, or holding dietary supplements to ensure the quality of the dietary supplement. The final rule is one of many actions related to dietary supplements that we are taking to promote and protect the public health.

**DATES:** This rule is effective [*insert date 60 days after date of publication in the Federal Register*].

*Compliance Dates:* The compliance date is [*insert date 12 months after date of publication in the Federal Register*]; except that for businesses employing fewer than 500, but 20 or more full-time equivalent employees, the compliance date is [*insert date 24 months after date of publication in the Federal Register*]; and except that for businesses that employ fewer than 20

1996N.0417  
CF0441

NFR 1

full-time equivalent employees, the compliance date is [*insert date 36 months after date of publication in the Federal Register*].

**FOR FURTHER INFORMATION CONTACT:** Vasilios H. Frankos, Center for Food Safety and Applied Nutrition (HFS-810), Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740, 301-436-1696.

**SUPPLEMENTARY INFORMATION:**

**Table of Contents**

I. Background and Related Information

II. How is the Final Rule Organized?

III. What Does the Final Rule Do?

A. Overview of CGMP

B. Highlights of the Final Rule

IV. What General Comments Did We Receive?

A. What Comments Did We Receive on the Structure and Organization of the Rule?

B. What Comments Did We Receive on the Need for Dietary Supplement CGMP Requirements?

C. What Comments Did We Receive on Written Procedures?

1. Overview

2. Written Procedures That Are Required by This Final Rule

3. Written Procedures That Are Not Required by This Final Rule

D. Other Comments on Written Procedures

E. What Other General Comments Did We Receive?

V. What Legal Authority Comments Did We Receive?

A. Modeled After CGMP for Food

B. Records Authority

C. Public Health Service Act Authority

1. The Communicable Disease Risk Posed by Dietary Supplements
2. Activities For Which We Are Asserting Legal Authority Under the PHS Act

D. The Interstate Commerce Nexus for the Final Rule

1. The PHS Act
  2. The Act
  3. Commerce Clause
- E. Fifth Amendment
- F. Miscellaneous

VI. What Comments Did We Receive on the General Provisions? (Subpart A)

- A. Organization of Final Subpart A
- B. Who Is Subject to This Part? (Final § 111.1)
- C. What Definitions Apply to This Part? (Final § 111.3)
  1. Actual Yield
  2. Batch
  3. Batch Number, Lot Number, or Control Number
  4. Component
  5. Contact Surface
  6. Ingredient
  7. In-Process Material
  8. Lot
  9. Microorganisms
  10. Must
  11. Pest
  12. Physical Plant
  13. Product Complaint
  14. Quality
  15. Quality Control
  16. Quality Control Personnel

17. Representative Sample

18. Reprocessing

19. Reserve Sample

20. Sanitize

21. Theoretical Yield

22. Water Activity

23. We

24. You

25. What Other Terms Did the Comments Want Defined?

26. What Definitions Did the Comments Want Us to Delete?

D. Do Other Statutory Provisions and Regulations Apply? (Final § 111.5)

E. What Sections Did We Remove From the Rule, and Why?

1. "What Are These Regulations Intended to Accomplish?" (Proposed § 111.2)

2. "Exclusions" (Proposed § 111.6)

VII. Comments on Personnel (Final Subpart B)

A. Organization of Final Subpart B

B. Highlights of Changes to the Proposed Requirements for Personnel

1. Revisions

2. Changes After Considering Comments

C. General Comments on Proposed Subpart B

D. What Are the Requirements Under This Subpart for Written Procedures?  
(Final § 111.8)

E. What Requirements Apply for Preventing Microbial Contamination  
From Sick or Infected Personnel and for Hygienic Practices? (Final  
§ 111.10)

1. Final § 111.10(a)

2. Final § 111.10(b)

F. What Personnel Qualification Requirements Apply? (Final § 111.12)

G. What Supervisor Requirements Apply? (Final § 111.13)

H. Under This Subpart, What Records Must You Make and Keep? (Final § 111.14)

VIII. Comments on Physical Plant and Grounds (Final Subpart C)

A. Organization of Final Subpart C

B. Highlights of Changes to the Proposed Requirements for Physical Plant and Grounds

1. Revisions

2. Changes After Considering Comments

C. General Comments on Proposed Subpart C

D. What Sanitation Requirements Apply to Your Physical Plant and Grounds? (Final § 111.15)

1. Final § 111.15(a)

2. Final § 111.15(b)(1)

3. Final § 111.15(c)

4. Final § 111.15(d)

5. Final § 111.15(e)

6. Final § 111.15(f)

7. Final § 111.15(g)

8. Final § 111.15(h)

9. Final § 111.15(i)

10. Final § 111.15(j)

11. Final § 111.15(k)

E. What Are the Requirements Under This Subpart for Written Procedures? (Final § 111.16)

F. What Design and Construction Requirements Apply to Your Physical Plant? (Final § 111.20)

1. Final § 111.20(a) and (b)
2. Final § 111.20(c)
3. Final § 111.20(d)
4. Final § 111.20(e)
5. Final § 111.20(f)
6. Final § 111.20(g)
7. Final § 111.20(h)

G. Under This Subpart, What Records Must You Make and Keep? (Final § 111.23)

IX. Comments on Requirements Related to Equipment and Utensils (Subpart D)

A. Organization of Final Subpart D

B. Highlights of Changes to the Proposed Requirements for Equipment and Utensils

1. Revisions
2. Revisions Associated With the Reorganization
3. Changes After Considering Comments

C. General Comments on Proposed Subpart D

D. What Are the Requirements Under This Subpart for Written Procedures? (Final § 111.25)

E. What Requirements Apply to the Equipment and Utensils That You Use? (Final § 111.27)

1. Final 111.27(a)
2. Final § 111.27(b)
3. Final § 111.27(c)
4. Final § 111.27(d)

F. Reorganization of Certain Paragraphs in Proposed § 111.25

G. What Requirements Apply to Automated, Mechanical, or Electronic

Equipment? (Final § 111.30)

1. Comments on the Organization and Framework of Proposed § 111.30
2. Comments Specific to Proposed § 111.30
3. Reorganization of Certain Paragraphs in Proposed § 111.30

H. Under This Subpart, What Records Must You Make and Keep? (Final § 111.35)

1. Final § 111.35(a)
2. Final § 111.35(b)(1) and (b)(2)
3. Final § 111.35(b)(3)
4. Final § 111.35(b)(4)
5. Final § 111.35(b)(5)
6. Final § 111.35(b)(6)

X. Comments on Requirement to Establish a Production and Process Control System (Final Subpart E)

- A. Reorganization of Proposed § 111.35 Into Final Subpart E
- B. General Comments on Proposed § 111.35
- C. Final Subpart E and Highlights of Changes to the Proposed Regulations
- D. What Are the Requirements to Implement a Production and Process Control System? (Final § 111.55)
- E. What Are the Design Requirements for the Production and Process Control System? (Final § 111.60)
- F. What Are the Requirements for Quality Control Operations? (Final § 111.65)
- G. What Specifications Must You Establish? (Final § 111.70)
  1. Final § 111.70(a)
  2. Final § 111.70(b)
  3. Final § 111.70(c)
  4. Final § 111.70(d)

5. Final § 111.70(e)

6. Final § 111.70(f)

7. Final § 111.70(g)

H. What is Your Responsibility for Determining Whether Established Specifications Are Met? (Final § 111.73)

I. What Must You Do to Determine Whether Specifications Are Met? (Final § 111.75)

1. Final § 111.75(a)

2. Final § 111.75(b)

3. Final § 111.75(c) and (d)

4. Final § 111.75(e)

5. Final § 111.75(f)

6. Final § 111.75(g)

7. Final § 111.75(h)

8. Final § 111.75(i)

J. What Must You Do if Established Specifications Are Not Met? (Final § 111.77)

1. Final § 111.77

2. Final § 111.77(a)

3. Final § 111.77(b)

4. Final § 111.77(c)

K. Comments on Shelf Life

L. What Representative Samples Must You Collect? (Final § 111.80)

1. Final § 111.80(a)

2. Final § 111.80(b)

3. Final § 111.80(c)

4. Final § 111.80(d)

5. Final § 111.80(e)

M. What Are the Requirements for Reserve Samples? (Final § 111.83)

1. Final § 111.83(a)
2. Final § 111.83(b)(1)
3. Final § 111.83(b)(2)
4. Final § 111.83(b)(3)
5. Final § 111.83(b)(4)

N. Who Conducts a Material Review and Makes a Disposition Decision?

(Final § 111.87)

O. What Requirements Apply to Treatments, In-Process Adjustments, and Reprocessing When There is a Deviation or Unanticipated Occurrence or When a Specification Established in Accordance With § 111.70 Is Not Met? (Final § 111.90)

1. Final § 111.90
2. Final § 111.90(a)
3. Final § 111.90(b)
4. Final § 111.90(c)

P. Under This Subpart, What Records Must You Make and Keep? (Final § 111.95)

1. Final § 111.95(a)
2. Final § 111.95(b)

XI. Comments on Requirements for Quality Control (Final Subpart F)

A. Organization of Final Subpart F

B. Highlights of Changes to the Proposed Requirements for Quality Control Operations

1. Revisions
2. Changes Associated With the Reorganization
3. Changes After Considering Comments

C. General Comments on Proposed § 111.37 (Final Subpart F)

D. What Are the Requirements Under This Subpart for Written Procedures?

(Final § 111.103)

E. What Must Quality Control Personnel Do? (Final § 111.105)

1. Final § 111.105(a)
2. Final § 111.105(b), (c), (d), and (e)
3. Final § 111.105(f)
4. Final § 111.105(g)
5. Final § 111.105(h)
6. Final § 111.105(i)

F. What Quality Control Operations Are Required for Laboratory

Operations Associated With the Production and Process Control System?

(Final § 111.110)

1. Final § 111.110(a)
2. Final § 111.110(b)
3. Final § 111.110(c)

G. What Quality Control Operations Are Required for a Material Review  
and Disposition Decision? (Final § 111.113)

1. Final § 111.113(a)
2. Final § 111.113(b)
3. Final § 111.113(c)

H. What Quality Control Operations Are Required for Equipment,  
Instruments, and Controls? (Final § 111.117)

1. Final § 111.117(a) through (c)
2. Final § 111.117(d)

I. What Quality Control Operations Are Required for Components,  
Packaging, and Labels Before Use in the Manufacture of a Dietary  
Supplement? (Final § 111.120)

1. Final § 111.120(a)
2. Final § 111.120(b)
3. Final § 111.120(c)

4. Final § 111.120(d)

5. Final § 111.120(e)

J. What Quality Control Operations Are Required for the Master

Manufacturing Record, the Batch Production Record, and Manufacturing Operations? (Final § 111.123)

1. Final § 111.123(a)(1)

2. Final § 111.123(a)(2)

3. Final § 111.123(a)(3)

4. Final § 111.123(a)(4)

5. Final § 111.123(a)(5)

6. Final § 111.123(a)(6)

7. Final § 111.123(a)(7)

8. Final § 111.123(a)(8)

9. Final § 111.123(b)

K. What Quality Control Operations Are Required for Packaging and Labeling Operations? (Final § 111.127)

1. Final § 111.127(a) and (b)

2. Final § 111.127(c)

3. Final § 111.127(d)

4. Final § 111.127(e)

5. Final § 111.127(f) and (g)

6. Final § 111.127(h)

L. What Quality Control Operations Are Required for Returned Dietary Supplements? (Final § 111.130)

1. Final § 111.130(a)

2. Final § 111.130(a)(1) and (a)(2)

3. Final § 111.130(b)

4. Final § 111.130(c)

5. Final § 111.130(d)

M. What Quality Control Operations Are Required for Product Complaints?

(Final § 111.135)

N. What Records Must You Make and Keep? (Final § 111.140)

1. Final § 111.140(a)
2. Final § 111.140(b)(1)
3. Final § 111.140(b)(2)
4. Final § 111.140(b)(3)

XII. Comments on the Production and Process Control System: Requirements for Components, Packaging, and Labels, and for Product That You Receive for Packaging or Labeling as a Dietary Supplement (Final Subpart G)

A. Organization of Final Subpart G

B. Highlights of Changes to the Proposed Requirements for Components, Packaging, and Labels, and Product That You Receive for Packaging or Labeling as a Dietary Supplement

1. Revisions
2. Changes After Considering Comments

C. General Comments on Proposed § 111.40 (Final Subpart G)

D. What Are the Requirements Under This Subpart for Written Procedures?

(Final § 111.153)

E. What Requirements Apply to Components of Dietary Supplements?

(Final § 111.155)

1. Proposed § 111.35(d)
2. Final § 111.155(a)
3. Final § 111.155(b)
4. Final § 111.155(c)
5. Final § 111.155(d)
6. Final § 111.155(e)

F. What Requirements Apply to Packaging and Labels Received? (Final

§ 111.160)

1. Final § 111.160(a)
2. Final § 111.160(b)
3. Final § 111.160(c)
4. Final § 111.160(d)
5. Final § 111.160(e)

G. What Requirements Apply to a Product Received for Packaging or Labeling as a Dietary Supplement (and for distribution rather than for return to the supplier)? (Final § 111.165)

1. Final § 111.165(a)
2. Final § 111.165(b)
3. Final § 111.165(c)
4. Final § 111.165(d)
5. Final § 111.165(e)

H. What Requirements Apply to Rejected Components, Packaging, and Labels, and to Rejected Products That Are Received for Packaging or Labeling as a Dietary Supplement? (Final § 111.170)

I. Under This Subpart, What Records Must You Make and Keep? (Final § 111.180)

1. Final § 111.180(a)
2. Final § 111.180(b)(1)
3. Final § 111.180(b)(2)
4. Final § 111.180(b)(3)

XIII. Comments on the Production and Process Control System: Requirements for the Master Manufacturing Record (Final Subpart H)

A. Organization of Final Subpart H

B. Highlights of Changes to the Proposed Requirements for the Master Manufacturing Record

1. Revisions

2. Changes Associated With the Reorganization

3. Changes After Considering Comments

C. General Comments on Proposed § 111.45 (Final Subpart H)

1. Comments on Written Procedures

2. Comments That Support Proposed § 111.45

D. What Is the Requirement to Establish a Master Manufacturing Record?

(Final § 111.205)

1. Final § 111.205(a)

2. Final § 111.205(b)(1)

3. Final § 111.205(b)(2)

4. Final § 111.205(c)

E. What Must the Master Manufacturing Record Include? (Final § 111.210)

1. Final § 111.210(a)

2. Final § 111.210(b)

3. Final § 111.210(c)

4. Final § 111.210(d)

5. Final § 111.210(e)

6. Final § 111.210(f)

7. Final § 111.210(g)

8. Final § 111.210(h)(1)

9. Final § 111.210(h)(2)

10. Final § 111.210(h)(3)

11. Final § 111.210(h)(4)

12. Final § 111.210(h)(5)

F. Quality Control Responsibility (Proposed § 111.45(c))

XIV. Comments on the Production and Process Control System: Requirements for the Batch Production Record (Final Subpart I)

A. Organization of Final Subpart I

B. Highlights of Changes to the Proposed Requirements for the Batch  
Production Record

1. Revisions
2. Changes Associated With the Reorganization
3. Changes After Considering Comments

C. What Is the Requirement to Establish a Batch Production Record? (Final  
§ 111.255)

D. What Must the Batch Record Include? (Final § 111.260)

1. Final § 111.260(a)
2. Final § 111.260(b)
3. Final § 111.260(c)
4. Final § 111.260(d)
5. Final § 111.260(e) and (f)
6. Final § 111.260(g)
7. Final § 111.260(h)
8. Final § 111.260(i)
9. Final § 111.260(j)
10. Final § 111.260(k)
11. Final § 111.260(l)
12. Final § 111.260(m)
13. Final § 111.260(n)

E. Review of Batch Production Record Deviations (Proposed § 111.50(d)(1),  
(e)(2), (e)(3), and (e)(4))

XV. Comments on Production and Process Control System: Requirements for  
Laboratory Operations (Final Subpart J)

A. Organization of Final Subpart J

B. Highlights of the Changes to the Proposed Requirements for Laboratory  
Operations

1. Revisions
2. Changes Associated With the Reorganization
3. Changes After Considering Comments
- C. What Are the Requirements Under This Subpart for Written Procedures?  
(Final § 111.303)
- D. What Are the Requirements for the Laboratory Facilities That You Use?  
(Final § 111.310)
- E. What Are the Requirements for Laboratory Control Processes? (Final § 111.315)
  1. Final § 111.315(a)
  2. Final § 111.315(b)
  3. Final § 111.315(c)
  4. Final § 111.315(d)
  5. Final § 111.315(e)
- F. What Requirements Apply to Laboratory Methods for Testing and Examination? (Final § 111.320)
  1. Final § 111.320(a)
  2. Final § 111.320(b)
- G. Appropriate Test Method Validation (Proposed § 111.60(b)(1)(v))
- H. Under This Subpart, What Records Must You Make and Keep? (Final § 111.325)
  1. Final § 111.325(a)
  2. Final § 111.325(b)(1)
  3. Final § 111.325(b)(2)

**XVI. Comments on the Production and Process Control System: Requirements for Manufacturing Operations (Final Subpart K)**

- A. Organization of Final Subpart K
- B. Highlights of Changes to the Proposed Requirements for Manufacturing

Operations

1. Revisions

2. Changes Made After Considering Comments

3. Revisions Associated With the Reorganization

C. General Comments on Manufacturing Operations

D. What Are the Requirements Under This Subpart for Written Procedures?

(Final § 111.353)

E. What Are the Design Requirements for Manufacturing Operations?

(Final § 111.355)

F. What Are the Requirements for Sanitation? (Final § 111.360)

G. What Precautions Must You Take to Prevent Contamination? (Final

§ 111.365)

1. Final § 111.365(a)

2. Final § 111.365(b)

3. Final § 111.365(c)

4. Final § 111.365(d)

5. Final § 111.365(e)

6. Final § 111.365(f)

7. Final § 111.365(g)

8. Final § 111.365(h)

9. Final § 111.365(i)

10. Final § 111.365(j)

11. Final § 111.365(k)

H. What Requirements Apply to Rejected Dietary Supplements? (Final

§ 111.370)

I. Under This Subpart, What Records Must You Make and Keep? (Final

§ 111.375)

XVII. Comments on the Production and Process Control System: Requirements for Packaging and Labeling Operations (Final Subpart L)

- A. Organization of Final Subpart L
- B. Highlights of Changes to the Proposed Requirements for Packaging and Labeling Operations
  - 1. Revisions
  - 2. Changes Associated With the Reorganization
  - 3. Changes After Considering Comments
- C. General Comments on Proposed Requirements for Packaging and Labeling Operations
- D. General Comments on Requirements for What Must Be on the Product Label Rather Than for Labeling Operations
- E. What Are the Requirements Under This Subpart for Written Procedures? (Final § 111.403)
- F. What Requirements Apply to Packaging and Labels? (Final § 111.410)
  - 1. Final § 111.410(a)
  - 2. Final § 111.410(b)
  - 3. Final § 111.410(c)
  - 4. Final § 111.410(d)
- G. What Requirements Apply to Filling, Assembling, Packaging, Labeling, and Related Operations? (Final § 111.415)
- H. What Requirements Apply to Repackaging and Relabeling? (Final § 111.420)
  - 1. Final § 111.420(a)
  - 2. Final § 111.420(b) and (c)
- I. What Requirements Apply to a Packaged and Labeled Dietary Supplement That Is Rejected for Distribution? (Final § 111.425)
- J. Under this Subpart, What Records Must You Make and Keep? (Final § 111.430)
  - 1. Final § 111.430(a)

2. Final § 111.430(b)

XVIII. Comments on Holding and Distributing (Final Subpart M)

A. Organization of Final Subpart M

B. Highlights of Changes to the Proposed Requirements for Holding and Distributing

1. Revisions

2. Changes Associated With the Reorganization

3. Changes After Considering Comments

C. General Comments on Proposed §§ 111.80, 111.82, 111.83, and 111.85

D. What Are the Requirements Under This Subpart for Written Procedures?  
(Final § 111.453)

E. What Requirements Apply to Holding Components, Dietary Supplements, Packaging, and Labels? (Final § 111.455)

1. Final § 111.455(a)

2. Final § 111.455(b)

3. Final § 111.455(c)

F. What Requirements Apply to Holding In-Process Material? (Final § 111.460)

1. Final § 111.460(a)

2. Final § 111.460(b)

G. Proposed Requirement for Holding Reserve Samples of Components  
(Proposed § 111.83(a))

H. What Requirements Apply to Holding Reserve Samples of Dietary Supplements? (Final § 111.465)

1. Final § 111.465(a)

2. Final § 111.465(b)

I. What Requirements Apply to Distributing Dietary Supplements? (Final § 111.470)

J. Under This Subpart, What Records Must You Make and Keep? (Final § 111.475)

XIX. Comments on Returned Dietary Supplements (Final Subpart N)

A. Organization of Final Subpart N

B. Highlights of Changes to the Proposed Requirements for Returned Dietary Supplements

1. Revisions

2. Changes After Considering Comments

C. General Comments on Proposed § 111.85

D. What Are the Requirements Under This Subpart for Written Procedures? (Final § 111.503)

E. What Requirements Apply When a Returned Dietary Supplement is Received? (Final § 111.510)

F. When Must a Returned Dietary Supplement be Destroyed, or Otherwise Suitably Disposed Of? (Final § 111.515)

G. When May a Returned Dietary Supplement Be Salvaged? (Final § 111.520)

H. What Requirements Apply to a Returned Dietary Supplement That Quality Control Personnel Approve for Reprocessing? (Final § 111.525)

I. When Must an Investigation Be Conducted of Your Manufacturing Processes and Other Batches? (Final § 111.530)

J. Under This Subpart, What Records Must You Make and Keep? (Final § 111.535)

1. Final § 111.535(a)

2. Final § 111.535(b)(1)

3. Final § 111.535(b)(2)

4. Final § 111.535(b)(3)

5. Final § 111.535(b)(4)

XX. Comments on Product Complaints (Final Subpart O)

A. Organization of Final Subpart O

B. Highlights of Changes to the Proposed Requirements for Product Complaints

1. Revisions

2. Changes After Considering Comments

C. General Comments on Proposed § 111.95 (Final Subpart O)

D. What Are the Requirements Under This Subpart for Written Procedures? (Final § 111.553)

E. What Requirements Apply to the Review and Investigation of a Product Complaint? (Final § 111.560)

1. Final § 111.560(a)(1)

2. Final § 111.560(a)(2), (b), and (c)

F. Under This Subpart, What Records Must You Make and Keep? (Final § 111.570)

1. Final § 111.570(a)

2. Final § 111.570(b)(1)

3. Final § 111.570(b)(2)

4. Final § 111.570(b)(2)(i)

5. Final § 111.570(b)(2)(ii)

XXI. Comments on Records and Recordkeeping (Final Subpart P)

A. Organization of Final Subpart P

B. Highlights of Changes to the Proposed Requirements for Records and Recordkeeping

1. Revisions

2. Changes After Considering Comments

C. General Comments on Proposed § 111.125

D. What Requirements Apply to the Records That You Make and Keep?

(Final § 111.605)

1. Final § 111.605(a)
2. Final § 111.605(b)
3. Final § 111.605(c)

E. What Records Must Be Made Available to FDA? (Final § 111.610)

1. Final § 111.610(a)
2. Final § 111.610(b)

## XXII. Other Comments and Miscellaneous

- A. Comments on Guidance Documents To Be Used With the Final Rule
- B. Comments on Consideration for Other CGMP Programs
- C. Comments on Public Involvement
- D. Comments on Implementation and Enforcement
- E. Removal of References to Part 112

## XXIII. Paperwork Reduction Act of 1995

## XXIV. Analysis of Impacts

### A. Introduction

1. Summary of the Economic Analysis
2. Summary of Comments on the Economic Analysis

### B. Final Regulatory Impact Analysis

1. The Need for the Final Current Good Manufacturing Practice Rule
2. Regulatory Options
3. Coverage of the Final Rule
4. Baseline Practices
5. Baseline Risk
6. Benefits
7. Costs
8. Summary of Benefits and Costs
9. Benefits and Costs of Regulatory Options
10. Cost Effectiveness Analysis

## 11. Uncertainties in the Analysis

### C. Final Regulatory Flexibility Analysis

#### 1. Introduction

#### 2. Economic Effects on Small Entities

#### 3. Regulatory Options

#### 4. Description of Recordkeeping and Reporting

#### 5. Summary

### D. Unfunded Mandates

## XXV. Analysis of Environmental Impact

## XXVI. Federalism

## XXVII. References

### **I. Background and Related Information**

On October 25, 1994, the Dietary Supplement Health and Education Act (DSHEA) (Public Law 103-417) was signed into law. DSHEA, among other things, amended the Federal Food, Drug, and Cosmetic Act (the act) by adding section 402(g) of the act (21 U.S.C. 342(g)). Section 402(g)(2) of the act provides, in part, that the Secretary of Health and Human Services (the Secretary) may, by regulation, prescribe good manufacturing practices for dietary supplements. Section 402(g) of the act also stipulates that such regulations shall be modeled after CGMP regulations for food and may not impose standards for which there are no current and generally available analytical methodology. The final rule establishes, in part 111 (21 CFR part 111), the minimum CGMPs necessary for activities related to manufacturing, packaging, labeling, or holding dietary supplements to ensure the quality of the dietary supplement. The final rule is one of many actions related to dietary supplements that we are taking to promote and protect the public health.

In response to DSHEA, we issued an Advance Notice of Proposed Rulemaking (the 1997 ANPRM) in the **Federal Register** of February 6, 1997 (62 FR 5700). The 1997 ANPRM contained a CGMP outline submitted to us on November 20, 1995, by representatives of the dietary supplement industry. The 1997 ANPRM also asked nine questions that addressed issues that the industry outline did not. For example, we asked if there is a need to develop specific defect action levels (DALs) for dietary ingredients. We also asked whether a CGMP rule should require manufacturers to establish procedures to document, on a continuing or daily basis, that they followed pre-established procedures for making dietary supplements.

We received more than 100 comments in response to the 1997 ANPRM. We evaluated these comments before we drafted and ultimately issued a proposed rule on CGMPs for dietary ingredients and dietary supplements (which we discuss later in this section of this document).

Additionally, during 1999, we conducted a number of outreach activities related to dietary supplements. We held several public meetings to develop our overall strategy for achieving effective regulation of dietary supplements, which could include establishing CGMP regulations. We also held public meetings focused specifically on CGMPs and the economic impact that any CGMP rule for dietary ingredients and dietary supplements might have on small businesses. Further, we toured several dietary supplement manufacturing facilities to better understand the manufacturing processes and practices that potentially would be subject to CGMP requirements for dietary ingredients and dietary supplements (Refs. 1 through 6). These activities contributed to our knowledge about the industry.

In the **Federal Register** of March 13, 2003 (68 FR 12157), we published a proposed rule to establish CGMP requirements for dietary ingredients and dietary supplements (the 2003 CGMP Proposal). The preamble to the 2003 CGMP Proposal addressed the comments we had received regarding the nine questions in the 1997 ANPRM, discussed our legal authority to issue a CGMP rule, and described the basis for each proposed requirement.

The 2003 CGMP Proposal specifically requested comment on a variety of areas, including the need for written procedures and recordkeeping requirements. Although the proposed rule's comment period was scheduled to end on June 11, 2003, in the **Federal Register** of May 19, 2003 (68 FR 27008), we extended the comment period to August 11, 2003.

After we published the proposed rule, we conducted and/or participated in outreach activities related to dietary supplements and dietary ingredients. We held public stakeholder meetings on April 29, 2003, in College Park, MD, and on May 6, 2003, in Oakland, CA. We also held a public meeting, via satellite downlink, on May 9, 2003, with viewing sites at our district and regional offices throughout the country. These public meetings gave an overview of the proposed rule, and clarified specific points in the proposed rule. Since the public stakeholder meetings held as part of our outreach efforts, we also have participated in several meetings with industry and other interested parties which are reflected in the public docket.

We received approximately 400 comments in response to the proposal. The comments came from trade associations, government organizations and officials, manufacturers of dietary supplements and dietary ingredients, health care practitioners, consumer groups, and individuals. In general, the comments

supported the idea of CGMPs, although many comments disagreed with specific aspects of the proposal.

Published elsewhere in this issue of the **Federal Register** we are also issuing an interim final rule that sets forth a procedure for requesting an exception to a CGMP requirement in this final rule. The interim final rule allows for submission to, and review by, FDA of an alternative to the required 100-percent identity testing of components that are dietary ingredients (as discussed in section X of this document (subpart E)), provided certain conditions are met. The interim final rule also includes a requirement for retention of records related to the FDA grant of an exception request.

## **II. How is the Final Rule Organized?**

The 2003 CGMP Proposal was divided into eight subparts, with each subpart devoted to a particular topic. For example, proposed subpart A was titled "General Provisions" and contained sections describing the rule's scope, purpose, definitions, applicability of other statutory and regulatory provisions, and exclusions. As another example, proposed subpart B was titled "Personnel" and described microbial contamination and hygiene requirements, personnel qualification requirements, and supervisor requirements.

In response to comments seeking a simpler, more "user-friendly" final rule or seeking clarification of the rule's applicability to certain persons, items, or activities, and to reduce redundant provisions or combine similar provisions, we have reorganized the final rule into 16 subparts, with new subparts focusing on specific aspects of the manufacturing process or addressing specific issues. For example, the proposed rule placed all production and process control requirements for manufacturing, packaging, labeling, and laboratory operations in a single subpart (proposed subpart E). The final rule creates separate

subparts for the specific operations to make it easier to find the relevant production and process control requirements for a particular activity.

Table 1 of this document summarizes how we reorganized the rule. We are providing this information to help readers understand the structural changes we made between the proposed and final rules.

TABLE 1.—REORGANIZATION AND REVISIONS: 2003 CGMP PROPOSAL AND FINAL RULE

Proposed Subpart and Title	Proposed Sections in the Subpart	Final Subpart and Title	Final Sections in the Subpart
A—General Provisions	111.1 111.2 111.3 111.5 111.6	A—General Provisions	111.1 111.3 111.5
B—Personnel	111.10 111.12 111.13	B—Personnel	111.8 (new) 111.10 111.12 111.13 111.14 (new)
C—Physical Plant	111.15 111.20	C—Physical Plant and Grounds	111.15 111.16 (new) 111.20 111.23 (formerly proposed § 111.15(d)(3) and (e)(2))
D—Equipment and Utensils	111.25 111.30	D—Equipment and Utensils	111.25 (formerly proposed § 111.25(c)(1) and (e)(1)) 111.27 (formerly proposed § 111.25 (a), (b), (d) <sup>1</sup> , and (e)) 111.30 111.35 (formerly proposed §§ 111.25 (c)(1), (c)(2), (d), (f), 111.30(b)(2), (b)(5), and (c), 111.50(c)(4))
E—Production and Process Controls	111.35 111.37 111.40 111.45 111.50 111.60 111.65 111.70 111.74	E—Requirement to Establish a Production and Process Control System	111.55 (formerly proposed § 111.35(a)) 111.60 (formerly proposed § 111.35(b)) 111.65 (formerly proposed § 111.35(c)) 111.70 (formerly proposed § 111.35(e), (f), (g), and (k)) 111.73 (formerly proposed § 111.35(f), (g), and (h)) 111.75 (formerly proposed § 111.35(e) through (i), (k), and (l)), § 111.37(b)(11)(iv), and § 111.40(a)(2) 111.77 (new) 111.80 (formerly proposed § 111.37(b)(11)) 111.83 (formerly proposed §§ 111.37(b)(12), 111.50(h), and 111.83(b)(2)) 111.87 (formerly proposed §§ 111.35(i) and (n), 111.37(b)(5) and (b)(14), 111.40(a)(3), 111.50(d)(1), and 111.85(a) and (c)) 111.90 (formerly proposed §§ 111.35(i)(4), 111.50(d)(1), (f), and (g), and 111.65(d)) 111.95 (formerly proposed § 111.35(o))

TABLE 1.—REORGANIZATION AND REVISIONS: 2003 CGMP PROPOSAL AND FINAL RULE—Continued

Proposed Subpart and Title	Proposed Sections in the Subpart	Final Subpart and Title	Final Sections in the Subpart
		F—Production and Process Control System: Requirements for Quality Control	111.103 (new) 111.105 (formerly proposed § 111.37(a), (b)(1), (b)(11), and (b)(12)) 111.110 (formerly proposed § 111.37(b)(9) and (b)(13)) 111.113 (formerly proposed §§ 111.35(i)(2), (i)(3), (i)(4)(i), (i)(4)(ii), (j), and (n), 111.37(b)(3) and (c), 111.40(a)(3) and (b)(2), 111.50(d)(1), 111.65(d), and 111.70(c)) 111.117 (formerly proposed §§ 111.30(b)(4) and 111.37(b)(6) through (b)(8)) 111.120 (formerly proposed §§ 111.35(i)(4)(i) and (i)(4)(ii), 111.37(b)(2) and (b)(10), 111.40(a)(3) and (b)(2), and 111.50(e)(1)) 111.123 (formerly proposed §§ 111.35(e)(2), (f), (f)(2), and (o)(2) 111.37(a), (b)(2), (b)(4), (b)(5), and (b)(11), 111.45(c), and 111.50(d)(1), (d)(2), and (g)) 111.127 (formerly proposed §§ 111.37(b)(2), (b)(10), and (b)(11), 111.40(a)(2) and (a)(3), and 111.70(c), (d) and (e)) 111.130 (formerly proposed §§ 111.37(b)(2) and (b)(15), and 111.85(a)) 111.135 (new) 111.140 (formerly proposed § 111.35(j) and 111.37(c) and (d))
		G—Production and Process Control System: Requirements for Components, Packaging, and Labels and for Product That You Receive for Packaging or Labeling a Dietary Supplement	111.153 (new) 111.155 (formerly proposed §§ 111.35(d)(1) through (d)(5) and 111.40(a)(1) through (a)(5)) 111.160 (formerly proposed §§ 111.35(e)(4), and 111.40(a)(2) and (b)(1) through (b)(4)) 111.165 (formerly proposed § 111.40(a)(1) through (a)(5)) 111.170 (formerly proposed § 111.74) 111.180 (formerly proposed §§ 111.35(d)(4), and 111.40(c)(1)(i) through (c)(1)(iv) and (c)(2))
		H—Production and Process Control System: Requirements for the Master Manufacturing Record	111.205 (formerly proposed § 111.45(a)(1), (a)(2), and (d)) 111.210 (formerly proposed § 111.45(b))
		I—Production and Process Control System: Requirements for the Batch Production Record	111.255 (formerly proposed § 111.50(a), (b), and (i)) 111.260 (formerly proposed §§ 111.35(i)(2), (j), (m), and (o)(2), 111.37(b)(3), (b)(5), (b)(9) and 111.50(c)(1) through (c)(11), (c)(13), (c)(14), (d)(2), (e), and (g), and 111.70(b)(6) and (g))
		J—Production and Process Control System: Requirements for Laboratory Operations	111.303 (new) 111.310 (formerly proposed § 111.60(a)) 111.315 (formerly proposed § 111.60(b)(1)) 111.320 (formerly proposed § 111.60(c) and (d)) 111.325 (formerly proposed § 111.60(b)(2) and (b)(3))

TABLE 1.—REORGANIZATION AND REVISIONS: 2003 CGMP PROPOSAL AND FINAL RULE—Continued

Proposed Subpart and Title	Proposed Sections in the Subpart	Final Subpart and Title	Final Sections in the Subpart
		K—Production and Process Control System: Requirements for Manufacturing Operations	111.353 (new) 111.355 (formerly proposed § 111.65(a)) 111.360 (formerly proposed § 111.65(b)) 111.365 (formerly proposed § 111.65(c)) 111.370 (formerly proposed § 111.74) 111.375 (new)
		L—Production and Process Control System: Requirements for Packaging and Labeling Operations	111.403 (new) 111.410 (formerly proposed § 111.70(a), (b)(6), and (f)) 111.415 (formerly proposed § 111.70(b)) 111.420 (formerly proposed § 111.70(d) and (e)) 111.425 (formerly proposed § 111.74) 111.430 (formerly proposed § 111.70(g) and (h))
F—Holding and Distributing	111.80 111.82 111.83 111.85 111.90	M—Holding and Distributing	111.453 (new) 111.455 (formerly proposed § 111.80) 111.460 (formerly proposed § 111.82) 111.465 (formerly proposed § 111.83(b)(1) and (b)(2)) 111.470 (formerly proposed § 111.90) 111.475 (new)
		N—Returned Dietary Supplements	111.503 (new) 111.510 (formerly proposed § 111.85(a)) 111.515 (formerly proposed § 111.85(b) and (c)) 111.520 (formerly proposed § 111.37(b)(15)) 111.525 (formerly proposed § 111.50(g)) 111.530 (formerly proposed § 111.85(d)) 111.535 (formerly proposed §§ 111.50(g) and 111.85(e) and (f))
G—Consumer Complaints	111.95	O—Product Complaints	111.553 (new) 111.560 (formerly proposed § 111.95(a) through (d)) 111.570 (formerly proposed § 111.95(e) and (f))
H—Records and Recordkeeping	111.125	P—Records and Recordkeeping	111.605 (formerly proposed § 111.125(a) and (b)) 111.610 (formerly proposed § 111.125(b) and (c))

<sup>1</sup>The reference to (d) is the second (d) in the proposed rule in this section due to a misnumbering in the proposed rule.

We discuss all subparts and sections, and our reasons for amending or creating subparts and sections, in our discussion of the comments to the proposal.

### III. What Does the Final Rule Do?

#### A. Overview of CGMP

In considering the specific requirements necessary for dietary supplement CGMPs, we considered information from a variety of sources. We considered

information from our outreach activities, as described in section I of this document; comments to the 2003 CGMP Proposal; our own knowledge and expertise about CGMP for foods, including dietary supplements; and characteristics of CGMP that apply to manufacturing, labeling, packaging, and holding operations.

The general food CGMPs in part 110 (21 CFR part 110) largely address practices designed to ensure that food is manufactured, processed, packed, and held under sanitary conditions and that the food is safe, clean, and wholesome. Although the general food CGMPs in part 110 apply to a variety of food products, including dietary supplements, they do not address the unique characteristics of certain specific types of food products. The agency has implemented separate, and more specific, CGMPs for various types of food products to provide for process controls in manufacturing that are not captured by the more general part 110 food CGMPs. (See discussion in section V of this document (“Legal Authority”) on product specific CGMP requirements). At the time DSHEA was enacted, there were four such additional, specific food CGMP regulations: Those for infant formula (part 106 (21 CFR part 106)), thermally processed low-acid canned food (part 113 (21 CFR part 113)), acidified food (part 114 (21 CFR part 114)), and bottled water (part 129 (21 CFR part 129)).

Dietary supplements are a type of food product for which specific food CGMPs also are needed. Manufacturing process controls are needed to ensure that a dietary supplement contains what the manufacturer intends. Unlike most foods, the majority of dietary supplements are packaged into tablets, gelcaps, and capsules. Some dietary supplements may contain bioactive ingredients for which certain, controlled amounts are intended to be in each tablet or capsule. The process controls that must be in place to ensure the tablet or capsule

contains what it purports to contain are different than those that must be in place to ensure a food is manufactured, processed, packed, and held under sanitary conditions. Process controls for dietary supplement manufacture include establishing and meeting specifications to ensure the finished dietary supplement contains the correct ingredient, purity, strength, and composition intended.

Vitamins can present a concentrated source of biologically active components. A vitamin, for example, that contains too high a concentration, such as vitamin D at levels that are many times greater than intended, can lead to illness and hospitalization (Refs. 7 and 8). A manufacturer must establish a process for manufacturing a dietary supplement product in order to produce the product consistently and reliably each time. In order to achieve consistency and reliability, there must be process controls in place to ensure, for example, that appropriate tests and examinations are conducted, a master manufacturing record is prepared, each batch production follows the master manufacturing record, and the finished tablet or capsule is placed in the intended package with the intended label.

These same types of controls are needed for herbal and botanical dietary supplements. Botanicals are often complex mixtures that can vary in composition depending on factors such as the part of the plant used, the location of harvesting and growing conditions that can vary from year to year even in the same location. It can be difficult to distinguish between closely related species of botanicals, and the biological activity of components of an incorrectly identified species can lead to adverse consequences. In addition, different species may be present in different ratios or blends in a particular product. Various products might contain different parts of the plant—flower,

leaf, root, stem, extract—and the test methods for each can vary in the nature, sensitivity, and specificity of the test.

Well-established principles of CGMP require process controls at each step of the manufacturing process as early in the production process as possible. Quality cannot be tested into the product only at the end (Ref. 9). Instead, the quality of the dietary supplement must be built into the product throughout the manufacturing process; quality begins with the starting material and continues with the product being manufactured in a reproducible manner according to established specifications. It is not sufficient, nor effective, to rely solely on end product testing to assure the quality of the individual dietary supplement product sold to the consumer.

CGMPs are intended to establish a comprehensive system of process controls, including documentation of each stage of the manufacturing process, that can minimize the likelihood of, or detect, problems and variances in manufacturing as they occur and before the product is in its finished form. These process controls that are a part of CGMPs are essential to ensure that the dietary supplement is manufactured, packaged, held, and labeled in a consistent and reproducible manner.

Manufacturing according to CGMP means that the manufacturing process incorporates a set of controls in the design and production processes to assure a quality finished product. CGMPs specific to dietary supplements are necessary to help ensure that these products have the identity, purity, strength, and composition that meet specifications established in the master manufacturing record and that they are not adulterated.

Many comments stressed that the most critical aspect of a successful CGMP system is effective process control. Comments asserted that, with

effective process control, quality is built into a product throughout the entire production process. The term “quality” came up repeatedly in comments as the desired outcome of the dietary supplement manufacturing process.<sup>1</sup> In fact, several comments asked us to define “quality” and suggested various definitions, each of which related to a dietary supplement having the identity, purity, strength, and composition intended (see comment 49 in section VI of this document). Some comments distinguished the concept of quality from that of preventing adulteration. These comments objected to our statement that dietary supplement CGMP requirements are needed to prevent adulteration and stated that CGMP is focused on assuring that finished products are manufactured using quality procedures, but are not related to preventing adulteration. Other comments asked us to define “adulteration.”

We agree that a critical aspect of CGMP is achieving control over manufacturing processes. Controls are necessary to ensure that you manufacture what you intend so that the characteristics and/or attributes desired in a final product will be consistently and reliably achieved. We disagree with the comments to the extent that they were suggesting that quality is not related to preventing contamination in the manufacturing process that may adulterate the finished product. However, we have reconsidered, as discussed in this section, what types of adulteration and misbranding are necessary to control for in this dietary supplement CGMP rule.

---

<sup>1</sup>Throughout this final rule, we refer to the “manufacture” or “manufacturing process” of dietary supplements. We use these terms in the broad sense, i.e., the terms refer to those activities that may be done from receipt of raw ingredients through the distribution of a finished dietary supplement, including labeling, packaging, and holding activities. We discuss the various roles and responsibilities of those who “manufacture” dietary supplements in the context of final § 111.1 “Who is subject to this part?” We also sometimes use the terms to apply to only part of the process, i.e., those operations other than labeling, packaging, and holding.

To clarify what dietary supplement CGMP requirements are intended to achieve, we have added a definition of quality in the final rule. As defined, quality means “that the dietary supplement consistently meets the established specifications for identity, purity, strength, and composition and has been manufactured, packaged, labeled, and held under conditions to prevent adulteration under section 402(a)(1), (a)(2), (a)(3), and (a)(4) of the Federal Food, Drug, and Cosmetic Act.” Ensuring the quality of the dietary supplement means that you consistently and reliably manufacture what you intend and that you establish manufacturing controls to prevent the dietary supplement from being adulterated under section 402(a)(1) of the act due to the presence of contaminants, under section 402(a)(2) of the act, for example, if it bears or contains any unintentionally added poisonous or deleterious substance, under section 402(a)(3) of the act if the dietary supplement consists in whole or in part of any filthy, putrid, or decomposed substance, or if it is otherwise unfit for food, or under section 402(a)(4) of the act if the dietary supplement has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. The definition of quality limits to section 402(a)(1), (a)(2), (a)(3), and (a)(4) of the act the types of adulteration that you must control for in this CGMP final rule. The definition applies to the controls that are designed to prevent contamination of the product that you intend to manufacture.

In the 2003 CGMP Proposal, we said that our purpose was to present a broad enough scope to the proposed rule so that we could receive the depth and breadth of comment needed to develop a final rule that would provide the proper balance of regulation (68 FR 12157 at 12161). We asked for comment on whether each of the provisions proposed was necessary to ensure the safety

and quality of the dietary supplement and was adequate to protect the public health (*id.*). We stated that the proposed rule “would establish the minimum CGMPs necessary to ensure that, if you engage in activities related to manufacturing, packaging, or holding dietary ingredients or dietary supplements, you do so in a manner that will not adulterate and misbrand such dietary ingredients or dietary supplements” (68 FR 12157 at 12158). For example, we stated that the proposed rule would require the manufacturer to test for toxic compounds in botanicals that may likely be present to ensure that no such compounds are present that may adulterate the dietary supplement (68 12157 FR at 12162). Further, we included a requirement that the ingredients, other than dietary ingredients under section 201(ff) of the act, be lawful under the applicable food additive regulations or be generally recognized as safe (GRAS) (proposed § 111.35(d)).

The approach that we set forth in the 2003 CGMP Proposal was designed to prevent a manufacturer, under CGMP regulations, from using an ingredient, whether a dietary ingredient or another component, in the manufacture of a dietary supplement that would adulterate the product under relevant provisions of the act, such as section 402(a)(1) or (a)(2)(C). The manufacturer would have been required to establish specifications at any point, step, or stage in the manufacturing process where control is necessary to prevent adulteration (proposed § 111.35(e)). Thus, the manufacturer would not have been able to establish a specification, consistent with proposed § 111.35(e), for the use of an unlawful ingredient because such use would not prevent adulteration. In addition, the manufacturer would have to establish specifications for contaminants that may adulterate or that could lead to adulteration of the dietary supplement. The manufacturer would have to take

necessary precautions to prevent the presence or level of contaminants, that would otherwise adulterate the dietary supplement under another provision of the act, from being present in the dietary supplement. The specifications were intended to ensure that adulterated and misbranded dietary supplements would not reach the marketplace (68 FR 12157 at 12197).

In addition to the general specifications established under proposed § 111.35(e), the proposed rule would have required the manufacturer to establish specifications for the identity, purity, quality, strength, and composition of the components received (proposed § 111.35(e)(1)) and for the finished batch of dietary supplement (proposed § 111.35(e)(3)). Although we stated that the proposed rule did not address questions related to the safety of dietary ingredients used (68 FR 12157 at 12172), if a dietary ingredient was deemed to be unsafe under the act—under section 402(a)(1) or another provision—a specification could not have been established for that dietary ingredient, consistent with proposed § 111.35(e). Thus, a manufacturer would not be able to use, under dietary supplement CGMP, a dietary ingredient, or other component, that would otherwise adulterate the product under another provision of the act.

Further, the proposed rule was designed to ensure that the correct label was applied during manufacture so that the dietary supplement label would accurately identify the dietary supplement (proposed §§ 111.45(b)(7), 111.50(c)(12), and 111.70(b)(7)). The proposed rule also would have required the master manufacturing record to contain the identity of each ingredient that is required to be declared on the ingredient list in section 403 of the act (21 U.S.C. 343) (proposed § 111.45(b)(4)).

Several comments seemed to question why the dietary supplement CGMP rule would require that a manufacturer use lawful ingredients when other provisions of the act would require such use. In fact, some comments objected to the proposed requirement in the rule that required that a component, other than a dietary ingredient, be approved for use as a food additive or be GRAS. The comments stressed that such a provision was not necessary because the statute already requires that such an ingredient be approved as a food additive or be GRAS. In light of these comments, we reconsidered our interpretation of the scope of “prevent adulteration” in the proposed rule and whether that interpretation should be narrowed. We also considered whether to require, as part of a CGMP requirement, that the label that accurately reflects the ingredients in the product be applied or whether such a requirement was not necessary, given our existing authority in section 403 of the act.

We determined that ensuring quality in dietary supplement CGMP, in part, means that you produce what you intend to produce. As stated in section V of this document, manufacturers must plan what they intend to produce, institute adequate controls to achieve the desired outcome, and ensure that the controls work so that the desired outcome is consistently achieved. Thus, for example, the manufacturer decides on the identity, purity, strength, and composition of the dietary supplement it manufactures. The focus of CGMP is on process controls to ensure that the desired outcome is consistently achieved, and not on the inherent safety of the ingredients used (which is addressed by other statutory prohibitions).

We agree with the comments that the safety of a particular ingredient is governed by other provisions of the act. If you manufacture a dietary supplement, you have a responsibility as a manufacturer to evaluate the safety

of the ingredients under, for example, section 402(f) of the act.<sup>2</sup> Dietary supplement CGMP would require you to establish the identity, purity, strength, and composition specifications for the product and ensure that such specifications are met in the finished batch of dietary supplement. Nothing in the dietary supplement CGMPs relieves manufacturers from complying with any other substantive provisions of the act relating to the safety of ingredients and other components.

Quality not only means that you produce what you intend, but that you prevent contamination in your manufacturing process that could adulterate your product. Food CGMP regulations, after which the dietary supplement CGMP rule is modeled, require that the manufacturer take precautions to ensure that the manufacturer does not adulterate the product under section 402(a)(1), (a)(2), (a)(3), and (a)(4) of the act. For example, under § 110.5 (food CGMP), the criteria and definitions apply in determining whether a food is adulterated under section 402(a)(3) and (a)(4) of the act. Specifically, § 110.80(a)(2) states that raw materials shall not contain levels of microorganisms that may produce food poisoning or other disease in humans, unless otherwise treated during manufacturing operations so that they no longer contain levels that would adulterate the product within the meaning of the act. In addition, § 110.80(a)(3) states that raw materials and other ingredients susceptible to contamination with natural toxins must comply with current FDA regulations and action levels for poisonous or deleterious substances before such materials are incorporated into finished food. Under dietary supplement CGMP, we believe it is appropriate to require you to

---

<sup>2</sup>Under section 402(f) of the act, a dietary supplement is deemed to be adulterated if it is or contains a dietary ingredient that presents a significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in labeling or, if no such conditions, under ordinary conditions of use.

establish specifications that are designed to prevent adulteration under section 402(a)(1), (a)(2), (a)(3), and (a)(4) of the act from contamination during the manufacturing, packaging, labeling, and holding operations. For example, if you are manufacturing a dietary supplement that you know is likely to contain a contaminant, you would need to establish limits on the contaminant in your supplement, and you must design these limits to prevent the dietary supplement from being adulterated under section 402(a)(1), (a)(2), (a)(3), and (a)(4) of the act.

Quality, as the term is used for the purposes of this final rule, relates both to producing what is intended (i.e., establishing and ensuring that specifications for the identity, purity, strength, and composition are met) and to ensuring that the dietary supplement that you intend to produce has been manufactured, packaged, labeled, and held under conditions to prevent adulteration within the meaning of section 402(a)(1), (a)(2), (a)(3), and (a)(4) of the act. Thus, this final rule is not designed to specifically prevent all types of adulteration that may occur under the act. Rather, this final rule is designed to prevent adulteration from those types of contamination that are commonly controlled in other food CGMP regulations. We do expect, however, that compliance with CGMP requirements in the final rule will help to avoid other types of adulteration. Also, nothing in this rule exempts a manufacturer from compliance with other relevant adulteration provisions of the act.

We are replacing the phrase “prevent adulteration” in the codified with words that relate to ensuring the quality of the dietary supplement. Thus, for example, we have modified proposed § 111.35(e) (now final § 111.70(a)) to read, “You must establish a specification for any point, step, or stage in the manufacturing process where control is necessary to ensure the quality of the

finished dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record” instead of “\* \* \* necessary to prevent adulteration.” This phrase is replaced in several codified provisions and an explanation of this change is not provided in the preamble of this document each time it is made.

Moreover, you have a responsibility under CGMP to ensure that the label you specify in the master manufacturing record is applied to the product. Under section 403 of the act, you are required to ensure that your label accurately reflects the ingredients in the product. Because section 403 of the act provides that food, including dietary supplements, is misbranded if a label that does not contain accurate statements is applied, we do not need to impose the same requirement in this final rule. Thus, if the representative label in the master manufacturing record for the product does not identify the correct dietary ingredients and the label that lists inaccurate information is applied, that dietary supplement would be misbranded under section 403 of the act. Such labeling would not be a violation of dietary supplement CGMP unless there is a mixup in your process control and you do not put the representative label specified in the master manufacturing record on the product. Such a mixup would be a violation of dietary supplement CGMP requirements (see e.g., final §§ 111.127(d), 111.160(e), 111.410(c), 111.415).

Thus, in addition to stating “ensure the quality of the dietary supplement,” in the codified instead of “prevent adulteration,” we are adding the language “and that the dietary supplement is packaged and labeled as specified in the master manufacturing record.” Such change is intended to clarify that the use of the packaging and labeling that is stated in the master manufacturing record is what is required in this final rule.

A failure to follow the requirements in this final rule, including a failure to establish required specifications, could result in an enforcement action by the agency under section 402(g) of the act because the dietary supplement is adulterated in that it was prepared, packed, labeled, or held under conditions that do not meet CGMPs for dietary supplements. The act establishes certain prohibited acts and enforcement mechanisms to remove adulterated product from the market and prevent manufacturers from continuing to manufacture adulterated product. Enforcement mechanisms currently available to us under the act are not affected by this final rule.

Finally, we have included in this final rule the existing requirements in part 110 that we believe are common to dietary supplement manufacturing. For example, the requirements in subpart C, *Physical Plant and Grounds*, are similar to those in § 110.20. We recognize that there may be operations related to the manufacturing of dietary supplements for which certain provisions in part 110 apply, but that we did not determine to be common to most dietary supplement manufacturing operations. For example, there may be some dietary supplements that are dehydrated and rely on the control of moisture consistent with § 110.80(b)(14). A manufacturer would be expected to comply with the regulations in part 110 in addition to the regulations in part 111, unless the regulations conflict. To the extent that the regulations conflict, the dietary supplement manufacturer must comply with the regulation in part 111.

#### *B. Highlights of the Final Rule*

The final rule:

- Applies to persons who manufacture, package, label, or hold dietary supplements unless subject to an exclusion in § 111.1;

- Establishes minimum requirements for personnel, physical plant and grounds, and equipment and utensils;
- Requires the establishment and use of written procedures for certain operations, including those related to equipment, physical plant sanitation, certain manufacturing operations, quality control, laboratory testing, packaging and labeling, and product complaints;
- Requires the establishment of specifications in the production and process control system that will ensure dietary supplements meet the identity, purity, strength, and composition established in specifications and are properly packaged and labeled as specified in the master manufacturing record;
- Provides for the option to use a certificate of analysis (for specifications other than the identity of a dietary ingredient) from a component supplier instead of having manufacturers conduct tests or examinations on the components they receive;
- Requires testing of a subset of finished batches of dietary supplements based on a sound statistical sampling or, alternatively, testing all finished batches;
- Requires implementation of quality control operations to ensure the quality of a dietary supplement;
- Requires the preparation and use of a written master manufacturing record for each unique formulation of manufactured dietary supplement, and for each batch size, to ensure your manufacturing process is performed consistently and to ensure uniformity in the finished batch from batch to batch;
- Requires the preparation of a batch production record every time a dietary supplement batch is made. The batch production record must accurately follow the appropriate master manufacturing record;

- Requires the establishment and use of laboratory control processes related to establishing specifications and to the selection and use of testing and examination methods;
- Requires reserve samples of dietary supplements to be held in a manner that protects against contamination and deterioration;
- Requires identification and quarantine of returned dietary supplements until quality control personnel conduct a material review and make a disposition decision;
- Requires quality control personnel to conduct a material review and make a disposition decision under certain circumstances;
- Requires a qualified person to investigate any “product complaint” that involves a possible failure of a dietary supplement to meet any CGMP requirement, with oversight by quality control personnel; and
- Requires records associated with the manufacture, packaging, labeling, or holding of a dietary supplement to be kept for 1 year beyond the shelf life dating (when such dating is used, such as expiration dating, shelf life dating, or “best if used by” dating), or if shelf life dating is not used, for 2 years beyond the date of distribution of the last batch of dietary supplements associated with those records.

#### **IV. What General Comments Did We Receive?**

We received approximately 400 comments on the proposed rule. Although most comments support CGMP requirements for dietary supplements and dietary ingredients, others question the need for a regulation and many sought changes to the rule. We describe, in this section, comments on general aspects of the final rule. We include comments related to the structure and organization of the final rule, comments we received on why CGMP requirements are needed, and comments on written procedures. In addition,

we describe some general comments we received on multiple sections of the proposed rule that we believe are better addressed in one response.

To make it easier to identify comments and our responses, the word “comment,” in parentheses, will appear before each comment, and the word “response” will appear before each response. We also have numbered the comments to make it easier to distinguish between comments; the numbers are for organizational purposes only and do not reflect the order in which we received the comments or any value associated with the comment.

*A. What Comments Did We Receive on the Structure and Organization of the Rule?*

(Comment 1) Several comments seek to restructure or reorganize the rule. For example, one comment states we should simplify the entire section on production and process controls. The comment asserts it would be more logical to list contaminants that may adulterate a dietary supplement or lead to adulteration as part of the requirements for specifications (proposed § 111.35(e)) than to list such contaminants as part of the testing requirements (proposed § 111.35(k)). Other comments say it would be more logical to list the tests that are considered appropriate as part of proposed § 111.35(h) (concerning appropriate tests or examinations to determine whether specifications are met) than to have a separate requirement for appropriate tests in proposed § 111.35(l) (which listed the types of analyses that should be part of a test).

Another comment claims the rule is too complex, asserting it would create chaos. Other comments say that the proposal’s degree of detail required is unrealistic for small dietary supplement firms, and we should rewrite the rule to be more user friendly.

Yet another comment says that any final rule we issue must clearly set forth CGMP requirements. This comment seems to suggest the requirements need to be more detailed in describing what is required. The comment asserts that ambiguities in interpretation could result in economic disadvantage for small businesses because they typically do not have in-house legal counsel and, thus, must be more conservative in interpreting ambiguous regulatory provisions.

(Response) In response to these comments, as well as comments on specific subparts and provisions, we have reorganized the final rule and have re-phrased or introduced concepts in a “user-friendly” or plain language format. We also have eliminated certain redundant regulatory requirements and combined similar requirements. For example, rather than put all production and process control system requirements in a single subpart, we have reorganized the final rule to create a series of subparts that first describe the requirements for the overall design and implementation of the production and process control system and then describe the requirements of the individual operations associated with that system. We also present each requirement as a question rather than as a paragraph within a section. This question format will help readers focus on the subparts or sections that apply to specific operations.

As another example, we reduced the redundancy associated with the interrelated nature of the proposed rule by combining most similar requirements. Both proposed §§ 111.35(m) and 111.60(b)(2) would require you to keep testing and examination results. The final rule places this requirement in a single section (§ 111.325(b)(2)(ii)).

The final rule also shortens the construction “includes, but is not limited to” to “includes.” We did this because the use of the word “includes” indicates that the specified list that follows is not exclusive. The phrase “but is not limited to” is unnecessary.

Finally, some changes we have made to one specific section have an impact on other sections. For example, after considering the comments, we revised subpart B to require you to establish and follow written procedures to fulfill the requirements of subpart B. Those written procedures are records you must make and keep in accordance with the recordkeeping requirements of subpart P, thus we made changes to include that requirement of making and keeping records.

*B. What Comments Did We Receive on the Need for Dietary Supplement CGMP Requirements?*

(Comment 2) Some comments state that dietary supplement CGMP requirements will protect consumers from supplements that contain inherently unsafe dietary ingredients. Other comments request that we take additional action to ensure the safety of dietary ingredients.

(Response) This final rule focuses on the manufacturing practices of dietary supplements and not on whether certain dietary ingredients are or are not safe. Therefore, comments related to whether certain dietary ingredients are inherently unsafe and any request to take actions related to the inherent safety of dietary ingredients are outside the scope of this rule.

(Comment 3) Some comments support the rule, explaining that it will address current problems with superpotent and subpotent dietary supplements, undeclared ingredients, and varying levels of ingredients. Others indicate the rule will better protect consumers and increase consumer

confidence. One comment states that CGMP requirements for dietary supplements are not needed for responsible manufacturers because they already manufacture safe dietary supplements. Some comments state that dietary supplement CGMP requirements are not needed because the dietary supplements have a track record of safety. Other comments say there were more adverse events reported from drug use than from dietary supplement use and that a large number of Americans take dietary supplements, and on that basis suggested that dietary supplements are safer than foods or drugs.

(Response) We agree the final rule will better protect consumers and help address the types of manufacturing problems identified in the preamble to the 2003 CGMP Proposal (see 68 FR 12157 at 12162 through 12163) through consistent use of established production processes and controls.

However, we disagree with the comments asserting dietary supplements have a track record of safety such that dietary supplement CGMP requirements are unnecessary. Section 402(g) of the act does not require us to establish a “bad” track record of safety in the manufacture of dietary supplements before we may issue a dietary supplement CGMP rule. Furthermore, we disagree with the comments comparing dietary supplement safety to drug safety; there are different statutory requirements, different regulatory requirements, and different safety evaluations for dietary supplements and drugs.

We also disagree that the final rule should apply only to manufacturers who cannot manufacture dietary supplements responsibly. Establishing who is or is not a responsible manufacturer is not a threshold requirement in section 402(g) of the act, and it would be impractical to regulate dietary supplement CGMP in such a manner, because parties may differ as to whether a particular manufacturer acted “responsibly” in a particular situation. All dietary

supplement manufacturers are subject to this final rule, just as all dietary supplement manufacturers are subject to section 402(g) of the act. We therefore are not persuaded that dietary supplement CGMP requirements are not needed, or should only be applied to manufacturers who have not acted “responsibly.”

(Comment 4) Some comments state that our authority under the current food CGMP regulation in part 110 and our authority to take actions against adulterated and misbranded products generally are sufficient. Other comments state that DSHEA gives us the necessary legal authority to protect the public health and that additional regulatory requirements are unnecessary. Several comments object to our statement that dietary supplement CGMP requirements are needed to prevent adulteration. These comments suggest dietary supplement CGMP is focused on ensuring finished products are manufactured using quality procedures, but are not related to preventing adulteration. Other comments state we should enforce current food CGMP regulations rather than adopt new regulations.

(Response) We disagree that dietary supplement CGMP requirements are not related to preventing adulteration. In fact, under the statutory scheme a dietary supplement is deemed to be adulterated under section 402(g)(1) of the act if it fails to meet CGMP requirements we promulgate by regulation. As we discussed in section III of this document, dietary supplement CGMP requirements are necessary to ensure the quality of the dietary supplement; ensuring quality includes ensuring that the dietary supplement has been manufactured, packaged, labeled, and held under conditions to prevent adulteration under section 402(a)(1), (a)(2), (a)(3), and (a)(4) of the act.

We also disagree with those comments stating that the requirements in part 110 are adequate and that no additional requirements are necessary. The

comments do not explain why the specific requirements set forth in the proposed rule that are not also in part 110 are unnecessary. As discussed in greater detail in response to comments on our legal authority in section V of this document, the particular characteristics and hazards of dietary supplements call for CGMP requirements tailored to dietary supplements. Congress specifically provided independent authority under section 402(g) of the act for us to promulgate CGMP requirements for dietary supplements. That authority would have been unnecessary if Congress had concluded that part 110 was adequate.

We also disagree that enforcement of part 110 would eliminate a need for dietary supplement CGMP requirements. The dietary supplement CGMP requirements include practices specifically tailored to the characteristics and hazards of dietary supplements and their manufacturers. The comments asserting that current food CGMP requirements in part 110 are sufficient provided no persuasive or compelling reasons for that assertion, or for why we should not implement dietary supplement CGMP requirements under section 402(g) of the act. For these reasons, we are not persuaded by the comments that these dietary supplement CGMP requirements are not needed.

(Comment 5) Some comments object to the examples of manufacturing problems that we used to support the need for CGMP requirements. Specifically, some comments object to the *Prevention* magazine citation and also object to the nine examples we presented in the preamble to the 2003 CGMP Proposal (see 68 FR 12157 at 12161 through 12163). We cited the *Prevention* magazine survey on consumer use of dietary supplements to show that only 41 percent of surveyed consumers who use vitamins and minerals think those products are very safe, and only 50 percent think the products

are somewhat safe; among those using herbal products, only 24 percent thought the products were very safe, and only 53 percent thought the products were somewhat safe. We noted that 74 percent supported increased government regulation of dietary supplements (see, *id.*). As one example of adulterated dietary supplements caused by manufacturing practices, the preamble to the 2003 CGMP Proposal mentioned an instance where a young woman suffered a life-threatening abnormal heart function that was traced to a mislabeled or contaminated dietary ingredient (68 FR 12157 at 12162). Another example involved recalls of super- and subpotent dietary supplements (*id.*).

Comments objecting to the *Prevention* survey said it provided no rationale for why CGMP requirements are needed. Other comments said the nine examples we provided represent a failure to conform to an existing regulation and do not demonstrate a need for a new CGMP regulation for dietary supplements. One comment disagrees that the CGMP requirements would prevent adverse reactions, as one example suggested in the preamble to the 2003 CGMP Proposal (see 68 FR 12157 at 12162) because, the comment claims, most adverse reactions are not the result of manufacturing problems. Another comment states the example involving plantain (68 FR 12157 at 12162), where a raw material was labeled as “plantain” when it was, in fact, *Digitalis lanata* (a plant that can cause life-threatening heart reactions), shows that, had there been a system in place to test finished product for purity and identity or to perform identity testing upon receipt, the manufacturer could have prevented that adulterated product from entering the market place. The comment states identity testing is necessary in the final rule.

Another comment objects to the example of “non-food grade chemicals” (*id.*) because the reference supporting the example involved Gamma-

Butyrolactone, a substance we have stated is an unapproved new drug and not a dietary supplement. Some comments say the risks cited in the justification for these regulations are hypothetical or theoretical and current statutory or regulatory authority is adequate.

(Response) We disagree, in most part, with the comments. We cited the *Prevention* survey to illustrate consumer perception and support for increased government involvement in dietary supplement regulation. We did not describe the survey as illustrating CGMP problems associated with dietary supplements.

We also disagree that the risks cited in the preamble to the 2003 CGMP Proposal are merely hypothetical or theoretical. We provided actual examples of failures in the manufacturing of products marketed as dietary supplements. The comments may have misunderstood what the CGMP requirements for dietary supplements are intended to accomplish. A principal goal of the CGMP requirements is to have those who manufacture, package, label, or hold dietary supplements do so in a manner that ensures the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record. It is the manufacturer who needs to establish procedures for its manufacturing operations to ensure, for example, the final product is produced according to its specifications in the master manufacturing record, meets limits on contaminants, and is a quality dietary supplement. If a product does not meet its specifications, a manufacturer who observes the CGMP requirements should know that and be able to take corrective action before the dietary supplement enters the marketplace. The onus is on the manufacturer, and not simply on us, to take action to prevent the adulterated product from entering the market or, if the product has already

been released, to remove the product from the market. The umbrella food CGMP requirements in part 110 do not contain specific provisions establishing specifications, requiring identity testing, or requiring in-process and/or finished product testing. Through this final rule, we are establishing a new CFR part regarding CGMP requirements specifically for dietary supplements.

The examples we used in the preamble to the 2003 CGMP Proposal included adverse event reports associated with contamination with *Digitalis lanata*, the possible contamination of botanical ingredients with toxic compounds, the use of non-food grade chemicals, the manufacture of super- and subpotent dietary supplements, the presence of undeclared ingredients, and the variability of ingredients from what is declared on the label (Refs. 7, 8, and 10; see, also, 68 FR 12157 at 12162 through 12163). These were all examples where products were manufactured, labeled, and sold to the consumer as dietary supplements. We disagree with the comments' assertions that all these problems can be adequately dealt with by the food CGMP requirements in part 110, but agree with the comment that, had there been a system in place "to perform identity testing upon receipt, the manufacturer could have prevented that adulterated product from entering the market place." Most of these examples present situations in which the manufacturer could have identified these problems through the dietary supplement CGMP requirements for specifications and testing or examination, such as identity verification, and could have prevented such products from entering the market or at least provided a greater assurance that such products would not make it into the marketplace. The dietary supplement CGMP requirements ensure adequate controls are in place to identify many of these types of manufacturing

errors before the product is in the marketplace and not through postmarketing adverse event reports or consumers' illnesses.<sup>3</sup>

The dietary supplement industry is diverse, as are the number and types of products marketed as dietary supplements. As we stated in the preamble to the 2003 CGMP Proposal (68 FR 12157 at 12163), given the wide range of public health concerns presented by the manufacturing practices for dietary supplements, a comprehensive system of controls is necessary. This final rule will set the standards for CGMP for dietary supplements that, if followed, will help ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record. The establishment of production and process controls and adherence to these and other CGMP requirements of this final rule will help to prevent the types of events (and others) we described in the nine examples presented in the preamble to the 2003 CGMP Proposal.

(Comment 6) Several comments suggest that dietary supplements are no different in safety or physiologic effect and require no different requirements than conventional food with respect to CGMP. One comment disagrees with us that dietary supplements require different requirements than conventional food because dietary supplements are ground up or in powder form and may not be easily recognized or differentiated; the comment says the same is true of many food ingredients as well.

(Response) We disagree with the suggestions by these comments that dietary supplement CGMP requirements need not differ from those for conventional foods. By definition, a dietary supplement is in a category of food

---

<sup>3</sup>Mandatory reporting to FDA of serious adverse events is now required as a result of the enactment of the "Dietary Supplement and Non-Prescription Drug Consumer Protection Act" (Public Law 109-462) signed into law on December 22, 2006 (see discussion in section XX of this document).

separate and distinct from the category of conventional food. The definition of dietary supplement in section 201(ff) of the act, in part, essentially describes a dietary supplement as a type of food that differs from conventional food. The definition refers to section 411(c)(1)(B)(i) and (c)(1)(B)(ii) of the act (21 U.S.C. 350(c)(1)(B)(i) and (c)(1)(B)(ii)), which describes the forms that dietary supplements intended to be ingested may take, i.e., tablet, capsule, powder, softgel, gelcap, or liquid form, and if not in such a form, limitations on how dietary supplements can be represented, i.e., not as conventional food or as a sole item of a meal or the diet.

Congress included separate additional provisions under section 402 of the act (see section 402(f) and (g) of the act) for when a dietary supplement may be adulterated. Congress considered that dietary supplements may warrant CGMP requirements that are different than those for conventional food. Although dietary supplements may include substances that are used as ingredients in conventional foods, the amounts consumed as a dietary supplement and as a conventional food product may not be the same and, in fact, may be more concentrated, and in higher amounts, when taken as a dietary supplement. The forms in which dietary supplements are consumed differ (e.g., capsule, tablet), as may the frequency, when compared to conventional foods. The uses of dietary supplements also differ from use as conventional food. Consequently certain manufacturing practices considered to be a part of CGMP for dietary supplement manufacturing may not be necessary for all types of food.

*C. What Comments Did We Receive on Written Procedures?*

## 1. Overview

In the 2003 CGMP Proposal (68 FR 12157 at 12165), we stated that written procedures were included in the dietary supplement CGMP outline submitted to us by industry, namely, the National Nutritional Foods Association standards (NNFA), the NSF International draft standards, and the United States Pharmacopoeia (USP) draft manufacturing practices. We also stated that, to limit the burden to manufacturers, we were not proposing to require written procedures for all the requirements. We invited comment on whether we should require written procedures for a variety of operations; specifically, for complying with the CGMP requirements, under proposed § 111.10 for personnel hygiene and for preventing microbial contamination due to personnel (68 FR 12157 at 12182); maintenance, cleaning, and sanitation for the physical plant under proposed § 111.15 (68 FR 12157 at 12187); calibrating instruments and controls under proposed § 111.25(b), (c), and (d) (68 FR 12157 at 12191); maintaining, cleaning, and sanitizing equipment and utensils under proposed § 111.25(e) (68 FR 12157 at 12192); calibrating, inspecting, and checking automatic equipment under proposed § 111.30 (68 FR 12157 at 12193); the duties of the quality control unit under proposed § 111.37 (68 FR 12157 at 12201); implementing the proposed requirements for receipt of components, dietary supplements, packaging, and labels under proposed § 111.40(a) and (b) (68 FR 12157 at FR 12203); preparing the master manufacturing record under proposed § 111.45 (68 FR 12157 at 12205); laboratory operations under proposed § 111.60 (68 FR 12157 at 12209); manufacturing operations under proposed § 111.65 (68 FR 12157 at 12211); packaging and labeling operations under proposed § 111.70 (68 FR 12157 at 12213); holding

components, dietary supplements, packaging, labels, and in-process materials under proposed §§ 111.80 and 111.82 (68 FR 12157 at 12214); identifying, quarantining, and salvaging returned dietary supplements under proposed § 111.85 (68 FR 12157 at 12216); and receiving, reviewing, and investigating consumer complaints under proposed § 111.95 (68 FR 12157 at 12217).

We stated that if comments assert that written procedures are necessary, comments should include an explanation of why the requirement is necessary to prevent adulteration including how such a requirement would ensure the identity, purity, quality, strength, and composition of the dietary supplement. Conversely, if comments assert that written procedures are not necessary, we asked for an explanation of why and how, in the absence of the requirement, one can prevent adulteration and ensure the identity, purity, quality, strength, and composition of the dietary supplement.

(Comment 7) Many comments stress the most critical aspect of a successful CGMP system is effective process control, which requires conducting key operations using written procedures. Several comments assert that written procedures are an important part of manufacturing operations to ensure uniform practices in production operations, from receiving through final operations. Several comments assert written procedures provide a sound basis for employee training and supervision. Several comments state that without a written training program, it is very likely that some employees may not receive sufficient training, or in some cases, any CGMP training at all. One comment specifically suggests that companies develop written procedures for the minimum CGMP training common to all departments.

One comment points out that all well-recognized quality systems require establishment of written procedures to ensure consistent process control, and

cites examples such as the International Organization for Standardization, the American National Standards Institute (ANSI), and the Malcolm Baldrige National Quality Award criteria. Other comments state that written procedures are necessary for the definition, operation, and documentation of a process control system, and that without such procedures it would be virtually impossible for any company, regardless of size, to consistently manufacture products that meet established requirements for identity, purity, quality, strength, and composition. The comments note that written procedures contain the necessary instructions for all employees to successfully execute their respective functions. Another comment supports a requirement for conducting key operations using written procedures and states that records document that operations were performed, but that written procedures show how the task is to be performed and at what frequency it should be performed. One comment states effective communication is essential to build quality into a process, and written procedures provide that throughout all levels of an organization. Another comment states it is difficult to imagine how the quality control unit could carry out its obligations under proposed § 111.37(b)(1) to “approve or reject all processes, specifications, controls, tests, and examinations, and deviations from or modifications to them \* \* \*” if these are not subject to written procedures.

Many comments which present one or more of these general reasons for requiring written procedures also list operations that they believe should be conducted using written procedures. The operations that one or more comments list as key operations are:

- Employee training;
- Cleaning the physical plant, including pest control;

- Maintenance, cleaning, and sanitizing of equipment and utensils;
- Calibration of equipment used in manufacturing or testing;
- All aspects of the production process, including a general procedure to document the minimum investigation, review, and approval requirements for failures in manufacturing or packaging operations;
  - All quality control operations;
  - Reprocessing of batches or start-up materials that do not conform to specifications;
  - Receipt, identification, examination, handling, sampling, testing, and approval or rejection of components, packaging, and labels;
  - Laboratory operations, including the establishment of specifications and descriptions of laboratory test methods used to ensure that components, in-process materials, and finished product meet established specifications;
  - Packaging and labeling operations, including issuance and use of appropriate labels, labeling, and packaging materials;
  - Holding and distribution procedures, including procedures for quarantine and parameters for storage;
  - Return and salvage operations;
  - Handling of consumer complaints; and
  - Procedures for product recall.

Many comments assert an effective process control system that includes extensive written procedures would justify a decreased testing burden with respect to the finished product. One comment suggests we exempt manufacturers from the requirement to test each finished batch of product if they have a qualified manufacturing process that meets certain basic criteria, including a requirement for written procedures for each stage of the process. One comment notes it would be clearer to all parties if specific written

procedures were listed as required and stresses the importance of having all companies know exactly what is procedurally expected of them.

In addition to these general reasons for requiring that key operations be conducted using written procedures, several comments provide specific reasons for requiring that specific operations be conducted using written procedures. In response to our request for comment on whether written procedures should be required for complying with proposed § 111.10 (personnel hygiene and for preventing microbial contamination due to personnel), one comment states that written procedures help to ensure compliance with the proposed hygiene requirements by clearly listing the requirements and requiring the employees to follow them on a consistent basis.

In response to our request for comment on whether written procedures should be required for complying with the proposed requirements for maintenance, cleaning, and sanitation for the physical plant under proposed § 111.15, one comment states that having written procedures in place to clean the physical plant will ensure that there is no cross-contamination. Another comment states utility areas such as effluent treatment, boilers, cooling towers, and water treatment plants also should have documented procedures for cleaning in order to create a general awareness of cleanliness throughout the plant. Other comments state that such written procedures should not be required because they would not directly prevent contamination or ensure the identity, purity, quality, strength, and composition of the dietary supplement if, as the "bottom line," a manufacturer maintains the physical plant in a clean and sanitary condition.

Responding to our request for comment on whether written procedures should be required for complying with the proposed requirements for

calibrating instruments and controls under proposed § 111.25(b), (c), and (d), several comments assert we should require manufacturers to establish and follow written procedures for calibrating equipment and controls. According to these comments, such procedures would provide us with a written record that is sufficient to evaluate the adequacy of the company's calibration procedures and would provide the necessary controls to meet the underlying intent of the rule. These comments assert that written procedures will lessen the risk that adulterated products will be produced.

In response to our request for comment on whether written procedures should be required for complying with the proposed requirements for maintaining, cleaning, and sanitizing equipment and utensils under proposed § 111.25(e), several comments assert such written procedures are crucial. These comments claim that written procedures promote consistency, clearly lay out expectations for employees, facilitate training, and provide a reference for individuals in performing their job functions. One comment states that written procedures for maintaining, cleaning, and sanitizing equipment are an industry standard.

In response to our request for comment on whether written procedures should be required for complying with the proposed requirements for preparing the master manufacturing record under proposed § 111.45, one comment states that written procedures for in-process control and quality checks should ensure the addition of the proper ingredients in the proper amount, and proper blending and control of other critical points. Another comment states written procedures are a critical element for ensuring consistent implementation of proper corrective action. Other comments state they do not support a requirement for written procedures for preparing the

master manufacturing record; and one comment suggests such a written procedure is not necessary because the proposed regulations for preparing the master manufacturing record already delineate the requirements for what information must be included in the master manufacturing record.

In response to our request for comment on whether written procedures should be required for complying with the proposed requirements for laboratory operations under proposed § 111.60, some comments specifically note the need for written procedures for the laboratory test methods used to ensure that components, in-process materials, and finished product meet established specifications. Some comments emphasize written procedures would create a standard for testing of products or groups of products and establishing parameters for passing or failing products.

In response to our request for comment on whether written procedures should be required for complying with the proposed requirements for manufacturing operations under proposed § 111.65, one comment asserts this is an effective way to train personnel and a means to hold operators accountable to a quality standard. Another comment states written procedures can improve quality and consistency in a manufacturing operation.

In response to our request for comment on whether written procedures should be required for complying with the proposed requirements for packaging and labeling operations under proposed § 111.70, one comment asserts this is an effective way to train personnel and a means to hold operators accountable to a quality standard.

Responding to our request for comment on whether written procedures should be required for complying with the proposed requirements for holding components, dietary supplements, packaging, labels, and in-process materials

under proposed §§ 111.80 and 111.82, one comment asserts this is an effective way to train personnel and a means to hold operators accountable to a quality standard. Another comment states a company cannot be considered to be a CGMP operation without having written procedures for every product manufacturing activity, including holding and distributing. This comment states mixups and adulterations will be more likely to occur if there are no written procedures for control of storage locations, manner of storage, and container and storage location identification codes.

In response to our request for comment on whether written procedures should be required for complying with the proposed requirements for returned dietary supplements, one comment states written procedures should govern all return and salvage operations to create a standard for quarantine and salvage and to establish parameters for proper salvage conditions.

Responding to our request for comment on whether written procedures should be required for complying with the proposed requirements for handling consumer complaints, some comments state written procedures will encourage companies to handle consumer complaints in a uniform manner. One comment asserts written procedures should be required for handling consumer complaints because some complaints could relate to serious illness or injury. The comment states that written procedures would set out exactly what steps need to be taken when complaints are reviewed, and are the best way to ensure the essential information is captured.

(Response) We agree with the comments that effective process control, using written procedures, is an important aspect of a successful CGMP program. We also agree requiring written procedures will help to ensure consistent practices in operations i.e., help to ensure the operation is

conducted in the same manner regardless of who conducts the operation or when the operation is conducted. We also agree that written procedures provide a sound basis for employee training and supervision, are an effective communication tool, and enable quality control personnel to carry out the responsibility to approve or reject all processes, specifications, controls, tests, and examinations, and deviations from or modifications to them. In addition, written procedures establish expectations for each covered operation so the operation does not proceed in an ad-hoc manner. Written procedures provide specific guidance if there is an unanticipated occurrence and, thus, can play a key role in ensuring a quality product, because actions to correct the unanticipated occurrence can take place swiftly and with confidence in the outcome.

This final rule establishes the minimum CGMPs necessary for activities related to manufacturing, packaging, labeling, and holding dietary supplements to ensure a quality product. The operations required by this final rule must be conducted in a consistent manner, regardless of who is conducting an operation or when the operation is conducted. As discussed in the following paragraphs, with a few exceptions, we are requiring that you establish and follow written procedures to fulfill the requirements for the operations covered by this final rule. The exceptions include final subpart A, which addresses the scope of the rule, rather than operations covered by the rule; final subparts E, H, and I, in which we conclude that a requirement for written procedures would be redundant to other requirements; and final subpart P, which establishes requirements for making and keeping records, rather than for conducting operations.

We believe requiring you to establish and follow written procedures to fulfill the requirements of subparts B through D, F, G, and J through O, when combined with other requirements of this final rule, justifies reduced requirements for testing finished batches of product compared to the proposed requirements for such testing as found in proposed § 111.35. By establishing and following written procedures, you will focus your production and process control system on ensuring the quality of the finished product at each stage in the production process, rather than relying entirely on testing at the end of the process.

## 2. Written Procedures That Are Required by This Final Rule

a. *Written procedures for personnel (final subpart B).* We believe that successful programs for process control are directly connected to appropriate training programs. Employee training must be conducted in a consistent manner, regardless of who conducts the training or when it is conducted. Failure to conduct employee training in a consistent manner could lead to a failure in ensuring product quality. For example, an employee who has not received appropriate training on how to conduct a specific physical examination to verify the identity of a dietary ingredient may erroneously report that the correct ingredient was received when, in fact, the received dietary ingredient is related to, but different from, the ingredient that is specified in the master manufacturing record.

We also believe the requirements that apply to preventing microbial contamination due to sick or infected personnel and that apply to proper hygienic practices must be conducted in a consistent manner. For example, it is well known that foodborne illness can be transmitted by workers who are sick. For example, volunteer food workers at an outdoor music festival were

found to be the source of contamination for an outbreak of *Shigellosis* (Ref. 11).

We include in final subpart B a requirement (final § 111.8) that you establish and follow written procedures for fulfilling the requirements of subpart B.

b. *Written procedures for cleaning the physical plant, including pest control (final subpart C).* We agree with the comments that written procedures for cleaning the physical plant would reduce the potential for cross-contamination and that such written procedures must include written procedures for pest control. Cleaning operations and pest control must be conducted in a consistent manner, regardless of who conducts the operation or when it is conducted. Failure to conduct cleaning operations and pest control in a consistent manner could lead to failure in ensuring product quality. For example, application of a chemical such as a fumigating agent or rodenticide in a production area must be performed correctly to avoid contaminating dietary supplements. Therefore, we disagree that written procedures would not directly prevent contamination or ensure the identity, purity, strength, and composition of the dietary supplement even if a manufacturer maintains the physical plant in a clean and sanitary condition.

We include in final subpart C a requirement that you establish and follow written procedures for cleaning the physical plant and for pest control (final § 111.16).

c. *Written procedures for calibrating instruments and controls and for calibrating, inspecting, and checking automated, mechanical, or electronic equipment (final subpart D).* Calibrating instruments and controls, and calibrating, inspecting, and checking automated, mechanical, or electronic

equipment must be conducted in a consistent manner, regardless of who conducts the operation or when it is conducted. Without a consistent approach, the performance of these operations could lead to equipment that produces inaccurate results. For example, if a scale is out of calibration, the wrong amounts of components could be added to a mixer. We include in final subpart D a requirement that you establish and follow written procedures for calibrating instruments and controls that you use in manufacturing or testing a component or dietary supplement (final § 111.25(a)) and for calibrating, inspecting, and checking automated, mechanical, and electronic equipment (final § 111.25(b)). We note that the manufacturers of equipment often provide written procedures for calibrating equipment. Depending on your circumstances and applications, you may be able to rely on written procedures provided by the manufacturer of the equipment with little or no modification.

Final § 111.25(a), pertaining to establishing and following written procedures for calibrating instruments and controls used in manufacturing or testing components or dietary supplements, is similar to proposed § 111.25(c)(1) which would provide an option, in relevant part, that you establish written procedures for calibrating such instruments and controls in addition to requiring you to document that the procedure was followed each time a calibration is performed.

d. *Written procedures for maintaining, cleaning, and sanitizing equipment and utensils (final subpart D).* Maintaining, cleaning, and sanitizing equipment and utensils must be conducted in a consistent and appropriate manner, regardless of who conducts the operation or when it is conducted. Failure to clean and sanitize equipment and utensils in a consistent and appropriate manner could lead to a product that is adulterated because, for example,

equipment and utensils that are not properly cleaned and sanitized could be a source of microorganisms, or could lead to cross-contamination of products. In addition, failure to maintain equipment in a consistent manner could lead to the failure to ensure product quality. For example, equipment that is properly maintained is less likely to malfunction than equipment that is not maintained, and using equipment that malfunctions could lead to errors in production, such as dispensing an incorrect amount of each ingredient.

We include in final subpart D a requirement that you establish and follow written procedures for maintaining, cleaning, and sanitizing equipment and utensils (final § 111.25(c)). Final § 111.25(c) applies to equipment, utensils, and any other contact surfaces used in labeling operations as well as in manufacturing, packaging, and holding operations. Although the factors you must consider for maintaining, cleaning, and sanitizing equipment used for labeling operations likely are different from those for equipment used in manufacturing or packaging operations, you nevertheless must determine the appropriate steps to take to ensure that labeling equipment is appropriately maintained and does not become a source of contamination for dietary supplements. For example, equipment used for labeling operations has a greater potential to contaminate a dietary supplement when labeling operations are carried out in concert with packaging operations, because the dietary supplement could be exposed to one or more contact surfaces during the packaging operations.

Final § 111.25(c) requires you to establish and follow written procedures for maintaining, cleaning, and sanitizing, as necessary, all equipment, utensils, and any other contact surfaces used to manufacture, package, label, or hold components or dietary supplements. Final § 111.25(c) relates to proposed

§ 111.25(e)(1) which would, in relevant part, require you to maintain, clean, and sanitize as necessary, all equipment, utensils, and contact surfaces used to manufacture, package, label, or hold components, dietary ingredients, or dietary supplements.

(Comment 8) Some comments suggest that written procedures for maintaining, cleaning, and sanitizing equipment require visual inspection of equipment when more than one product is manufactured using the same equipment, and that the presence of residual components from one product in a different product could be harmful. The comments also suggest the written procedures include residual limits of components from different product lines to guarantee the safety of the dietary supplement.

(Response) The final rule gives you flexibility to develop written procedures appropriate to your products and equipment. Consequently, final § 111.25(c) neither requires nor prohibits any specific procedure, such as the visual inspection suggested by the comment.

As for the residual limits, the comment provides no data or other information that would provide a basis for setting residual limits for any particular components. However, as we discuss more fully in the discussion of final § 111.70(e) in section X of this document, the final rule requires you to establish and meet specifications for the identity, purity, strength, and composition of dietary supplements and for limits on contamination for dietary supplements that you manufacture. When considering the specifications you must establish to ensure the quality of the dietary supplements, you must take into account the need to ensure that components or dietary supplements are not contaminated as a result of using the same equipment. Such equipment

could be a source of contamination if more than one product is manufactured using the equipment and it is not properly cleaned and/or sanitized.

*e. Written procedures for quality control operations, including written procedures for conducting a material review and making a disposition decision and written procedures for approving or rejecting reprocessing (final subpart F).* Quality control operations must be conducted in a consistent manner.

Failure to carry out quality control operations in a consistent and appropriate way could lead to failure to ensure product quality and to ensure the dietary supplement is packaged and labeled as specified in the master manufacturing record. For example, you could use a component that should not have been released for use in manufacturing, or you could distribute a packaged and labeled dietary supplement that should not have been released for distribution.

We include in final subpart F a requirement that you establish and follow written procedures for quality control operations (final § 111.103). We agree with the comments that there should be written procedures for investigating failures in manufacturing operations. In the 2003 CGMP Proposal, we referred to the process of investigating such failures as a “material review” and proposed a series of requirements related to a material review and the disposition decision that follows a material review. The review must be conducted in a consistent manner, and the criteria for making a disposition decision must be consistent, regardless of who is conducting the material review or when it is conducted, and regardless of who makes the disposition decision and when the decision is made. For example, if you do not have written criteria for determining whether a deviation from specifications has resulted in, or could lead to, adulteration, different individuals who conduct a material review could reach different decisions regarding the appropriate

disposition of the affected dietary supplement, including decisions that incorrectly result in the release of an adulterated product. As discussed more fully in sections X and XI of this document, the final rule requires that quality control personnel conduct all required material reviews and make all required disposition decisions. Therefore, we are requiring that the written procedures for quality control operations include written procedures for conducting a material review and making a disposition decision (final § 111.103).

We considered the comments that suggest that there should be a requirement for you to establish and follow written procedures for reprocessing from two perspectives: (1) Determining whether reprocessing should be approved or rejected and (2) performing the reprocessing. In general, reprocessing is performed when there is a problem with the manufacturing process, such as when a specification is not met or any step in the master manufacturing record is omitted. Depending on the nature of the dietary supplement, the manufacturing process, and the problem, reprocessing may or may not be able to correct the problem. From the perspective of determining whether reprocessing should be approved or rejected, under the final rule it is quality control personnel who must approve or reject any reprocessing (see final §§ 111.90, 111.113, 111.120, 111.123, and 111.130). The decision to approve reprocessing must be made in a consistent manner, regardless of who conducts the operation or when it is conducted. For example, if it is not possible to test the product at the finished batch stage to determine whether the reprocessing corrected the problem (because, for example, there is no scientifically valid method available to test for a specification that is directly related to the reason for reprocessing), you must have a clear basis to decide that reprocessing will actually correct the problem or you will not know if

all required specifications can be met. Without written procedures for approving reprocessing, different individuals who approve or reject any reprocessing could make very different decisions on when reprocessing can correct a problem and when it cannot. Therefore, we are specifically requiring that the written procedures for quality control operations include written procedures for approving or rejecting any reprocessing.

From the perspective of performing the reprocessing, we agree that any procedure for reprocessing must be written because, for example, quality control personnel may need to rely on the procedure that you followed to determine whether all specifications are met for the reprocessed material. However, the final rule requires you to document any reprocessing in the batch record (final § 111.260(n)) rather than establishing and following written procedures to conduct reprocessing, because the actual procedure you follow to reprocess a dietary supplement likely will be different depending on the circumstances.

*f. Written procedures for components, packaging, labels, and product that is received for packaging and labeling as a dietary supplement (final subpart G).* We agree with the comments that the receipt, examination, quarantine, and release from quarantine of components, packaging, labels, and product that are received for packaging and labeling as dietary supplements must be conducted in a consistent manner, regardless of who conducts the operation or when it is conducted. Failure to carry out these operations in a consistent way could lead to failure to ensure product quality if, for example, you use a component that should not have been released for use in manufacturing.

We include in final subpart G a requirement that you establish and follow written procedures for fulfilling the requirements of subpart G (final § 111.153).

g. *Written procedures for laboratory operations (final subpart J).* Testing and examination of components, packaging, labels, and product that are received for packaging or labeling as a dietary supplement, or packaged and labeled dietary supplements, must be conducted in a consistent manner, regardless of who conducts the operation or when it is conducted. The reason a firm conducts these tests and examinations is to ensure that a dietary supplement meets established specifications. Failure to conduct tests and examinations in a consistent manner could lead to failure in ensuring the quality of the dietary supplement. For example, a test designed to determine the concentration of a product before it is diluted to the appropriate concentration could provide different results if it is conducted in a different manner by different individuals.

In addition, laboratory operations such as use of criteria for establishing appropriate specifications and use of sampling plans for obtaining representative samples must be conducted in a consistent manner, regardless of who conducts the operation or when it is conducted. For example, failure to consider that specifications are needed to ensure that a dietary supplement derived from a botanical source does not contain contaminants, such as an unlawful pesticide, could result in a dietary supplement that contains unsafe levels of a contaminant.

We include in final subpart J a requirement that you establish and follow written procedures for laboratory operations, including written procedures for the tests and examinations that you conduct to determine whether specifications are met (final § 111.303).

h. *Written procedures for manufacturing operations (final subpart K).* We agree with the comments that written procedures for manufacturing operations

would be an effective way to train personnel, provide a means to hold operators accountable to a quality standard, and improve quality and consistency in a manufacturing operation. The final provisions for manufacturing operations require you to design or select manufacturing processes to ensure that dietary supplement specifications are consistently achieved, conduct all manufacturing operations in accordance with adequate sanitation principles, and take all necessary precautions to prevent contamination of components and dietary supplements. These manufacturing operations must be conducted in a consistent manner, regardless of who conducts the operation or when it is conducted. Failure to perform these operations in a consistent way could lead to failure to ensure the quality of the dietary supplement. For example, surfaces that come in contact with a dietary supplement are potential sources of microbial contamination if consistent procedures are not in place to ensure good sanitary practices. We are including in final subpart K a requirement that you establish and follow written procedures for manufacturing operations (final § 111.353).

i. *Written procedures for packaging and labeling operations (final subpart L).* We agree with the comments that written procedures for packaging and labeling operations are an effective means to hold operators accountable to ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record. The final provisions for packaging and labeling operations require that you fill, assemble, package, label, and perform other related operations in a way that ensures the quality of the finished product, including practices such as cleaning and sanitizing all filling and packaging equipment, utensils, and containers; protecting manufactured dietary supplements against airborne

contamination, using sanitary handling procedures; taking actions to prevent mixups; and suitably disposing of obsolete packaging and labels. These packaging and labeling operations must be conducted in a consistent manner, regardless of who conducts the operation or when it is conducted. Failure to perform these operations in a consistent way could lead to a failure to ensure the quality of the dietary supplement and that the dietary supplement is labeled and packaged as specified in the master manufacturing record. For example, if you do not have procedures for identifying filled, but unlabeled, containers of dietary supplements, mixups could occur before the labels are applied. The final product could contain ingredients other than those identified on the label specified in the master manufacturing record. Therefore, we include in final subpart L a requirement that you establish and follow written procedures for packaging and labeling operations (final § 111.403).

j. *Written procedures for holding and distributing operations (final subpart M).* We agree with the comments that written procedures for holding and distributing operations are an effective means to hold operators accountable to CGMP standards, and that mixups and other problems that affect the final product will be more likely to occur if there are no written procedures for operations such as control of storage locations, manner of storage, and container and storage location identification codes. The final provisions for holding and distributing operations require, among other things, that you hold components and dietary supplements under appropriate conditions of temperature, humidity, and light so that the identity, purity, strength, and composition of the components and dietary supplements are not affected; that you hold components, dietary supplements, and in-process materials under conditions that do not lead to the mixup, contamination, or deterioration of

components or dietary supplements; and that you distribute dietary supplements under conditions that will protect them against contamination and deterioration.

These holding and distributing operations must be conducted in a consistent manner, regardless of who conducts the operation or when it is conducted. Failure to follow these requirements for holding and distributing in a consistent manner could lead to a failure to ensure the quality of the dietary supplement product. For example, if employees do not know how to store an in-process batch of a botanical dietary supplement to control humidity, the growth of mold could be promoted. Furthermore, if a distributor does not refrigerate a dietary supplement that requires refrigeration to ensure its strength, the dietary supplement may not meet its specification for strength. Therefore, we include in final subpart M a requirement that you establish and follow written procedures for holding and distributing operations (final § 111.453).

k. *Written procedures for returned dietary supplements (final subpart N).*

We agree with the comments that written procedures for returned dietary supplements would help to ensure appropriate handling of such supplements prior to a disposition decision. The final rule requires you, among other things, to identify and quarantine returned dietary supplements until quality control personnel conduct a material review and make a disposition decision. You must destroy, or otherwise suitably dispose of, any returned dietary supplement that quality control personnel do not approve for salvage or reprocessing. These operations for returned dietary supplements must be conducted in a consistent manner, regardless of who conducts the operation or when it is conducted. Failure to comply with these requirements for

quarantine, salvage, and disposition in a consistent way could lead to a failure to ensure the quality of the dietary supplement. For example, if an investigation leads to a conclusion that a dietary supplement requiring refrigeration to ensure its strength was not refrigerated while held at a customer's warehouse, and this dietary supplement was not quarantined while quality control personnel conducted a material review, the dietary supplement could be inadvertently co-mixed with other containers of that same lot of product and then inadvertently redistributed. Therefore, we are including in final subpart N a requirement that you establish and follow written procedures to fulfill the requirements of subpart N (final § 111.503).

1. *Written procedures for product complaints (final subpart O)*. We agree with the comments that written procedures for handling consumer complaints (now called product complaints) will encourage companies to handle product complaints in a consistent manner and help ensure the essential information is captured during investigation of a product complaint. The final rule requires you, among other things, to review all product complaints to determine whether the product complaint involves a possible failure of a dietary supplement to meet any of its specifications; investigate any product complaint that involves a possible failure of a dietary supplement to meet any of its specifications; and extend the review and investigation of the product complaint to all relevant batches and records. These operations must be conducted in a consistent manner, regardless of who conducts the operation or when it is conducted. Failure to comply with these requirements for review and investigation of a product complaint in a consistent way could lead to a failure to ensure the quality of the dietary supplement. For example, if you do not have a procedure in place to determine whether the product complaint

involves a possible failure of a dietary supplement to meet any of its specifications, you may not recognize that a particular product complaint is indicative that a problem has occurred with one of your manufacturing processes. That undiscovered problem may lead to continued distribution of product that is contaminated or otherwise not consistent with your specifications in the master manufacturing record. Therefore, we include in final subpart O a requirement that you establish and follow written procedures to fulfill the requirements of subpart O (final § 111.553).

### 3. Written Procedures That Are Not Required by This Final Rule

a. *Written procedures for final subpart E (“Requirement to Establish a Production and Process Control System”)*. In the CGMP proposal, we did not specifically request comments on whether we should require that you establish and follow written procedures to fulfill the requirements of proposed § 111.35 (“What Production and Process Controls Must You Use?”), and we received no specific comments regarding whether we should establish and follow such written procedures. Given the strong support in the comments for the use of written procedures in a production and process control system, we nonetheless considered whether the requirements that we establish in final subpart E, *Requirement to Establish a Production and Process Control System*, would require written procedures.

Final subpart E requires that you implement a system of production and process controls that covers all stages of manufacturing, packaging, labeling, and holding of the dietary supplements and that your system be designed to ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in your master manufacturing record (final §§ 111.55 and 111.60); implement quality control operations to ensure the

quality of dietary supplements and that the dietary supplement is packaged and labeled as specified in your master manufacturing record (final § 111.65); establish specifications (final § 111.70); determine whether specifications are met (final §§ 111.73 and 111.75); collect representative samples (final § 111.80); hold reserve samples of packaged and labeled dietary supplements (final § 111.83); have quality control personnel conduct all required material reviews and make all required disposition decisions (final § 111.87); and adhere to certain requirements for treatment, in-process adjustments, and for reprocessing (final § 111.90).

In considering whether we should require that you establish and follow written procedures to fulfill the requirements of final subpart E, we evaluated whether requirements in other subparts that address specific operations for the production and process control system substitute for the requirement of written procedures in final subpart E.

Final subparts F through M establish specific requirements for manufacturing, packaging, labeling, and holding dietary supplements, including requirements for quality control operations (final subpart F); components, packaging, labels, and product that is received for packaging and labeling as a dietary supplement (final subpart G); establishing a written master manufacturing record and batch record (final subparts H and I); laboratory operations (final subpart J); manufacturing operations (final subpart K); packaging and labeling operations (final subpart L); and holding operations (final subpart M). We require you to establish and follow written procedures to fulfill the requirements of final subparts F, G, J, K, L, and M. Given these requirements, we conclude it would be redundant to require you to establish

and follow written procedures to fulfill the requirements of final §§ 111.55, 111.60, and 111.65 in subpart E.

Final subpart J requires you to establish and follow laboratory control processes that include the use of criteria for establishing appropriate specifications (final § 111.315(a)); use of sampling plans for obtaining representative samples (final § 111.315(b)); use of criteria for selecting appropriate examination and testing methods (final § 111.315(c)); use of criteria for selecting standard reference materials used in performing tests and examinations (final § 111.315(d)); and use of test methods and examinations in accordance with established criteria (final § 111.315(e)). In addition, under final § 111.303 you must establish and follow written procedures for laboratory operations. Given the requirements of final subpart J, we conclude it would be redundant to require you to establish and follow written procedures to fulfill the requirements of final §§ 111.70, 111.75, and 111.80 in subpart E.

Final subpart M establishes requirements for holding reserve samples. Under final § 111.453, you must establish and follow written procedures for holding operations. Given the requirements of final subpart M, we conclude that it would be redundant to require you to establish and follow written procedures to fulfill the requirements of final § 111.83 in subpart E for reserve samples.

Final subpart F establishes requirements for quality control personnel to conduct a material review and make a disposition decision (final § 111.113); approve any reprocessing (final § 111.123(a)(5)); and document any material review and disposition (final § 111.140(b)(3)). In addition, as discussed, under final § 111.103 you must establish and follow written procedures for quality control operations. Given the requirements of final subpart F, we conclude that

it would be redundant to require that you establish and follow written procedures to fulfill the requirements of final §§ 111.87 and 111.90 in subpart E.

We conclude that it would be redundant to require you to establish and follow written procedures for each of the requirements established in final subpart E. We, therefore, do not require you to establish and follow written procedures to fulfill the requirements established in subpart E.

b. *Written procedures for preparing the master manufacturing record (final subpart H) and for preparing the batch record (final subpart I).* As discussed in the 2003 CGMP Proposal (68 FR 12157 at 12203), a master manufacturing record is analogous to a recipe that sets forth the ingredients to use, the amounts of ingredients to use, the tests to perform, and the instructions for preparing the quantity the recipe calls for. This master manufacturing record helps ensure that you manufacture each ingredient or dietary supplement in a consistent and uniform manner. If you neglect to follow the master manufacturing record, you might not add all of the necessary components in the appropriate strength or amount, and this could result in a final product not consistent with the master manufacturing record. Thus, you must follow a written master manufacturing record in a consistent manner, regardless of who conducts the operation or when it is conducted.

However, we agree with the comments that the specific requirements for what must be in the master manufacturing record make it unnecessary to require written procedures for preparing the master manufacturing record. Under final subpart H, the master manufacturing record must include written instructions, including specifications for each point, step, or stage in the manufacturing process where control is necessary to ensure the quality of the

dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record; procedures for sampling, testing, and examinations; specific actions necessary to perform and verify points, steps, or stages in the manufacturing process where control is necessary to ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record; special notations and precautions to be followed; and corrective action plans for use when a specification is not met. With all of this detail specified for the written instructions the master manufacturing record must include, we believe a written procedure for developing a master manufacturing record can be optional. Therefore, we do not require you to establish and follow written procedures for preparing the master manufacturing record.

A batch is prepared by following the written instructions provided in the master manufacturing record. The master manufacturing record functions as a written procedure for the production of the batch. Therefore, we do not require you to establish and follow written procedures for the batch production record because such practices would be redundant to the requirements for the master manufacturing record in final subpart H.

*c. Written procedures for records and recordkeeping (final subpart P).*

Final subpart P establishes general requirements for making and keeping records required in other subparts. We did not request comments on written procedures, nor did we receive any comments that supported such a requirement. Because we believe that requiring written procedures to fulfill subpart P requirements would be redundant or unnecessary, we do not require such written procedures.

d. *Written procedures for product recalls.* We acknowledge that a product recall by persons who manufacture, package, label, or hold dietary supplements must be conducted in a consistent manner, regardless of who conducts the operation or when it is conducted. However, the final rule does not establish any requirements for product recalls. Therefore, we do not require you to establish and follow written procedures for product recalls. However, we encourage you to refer to our “Guidance for Industry: Product Recalls, Industry Removals and Corrections” (Ref. 12) (available at <http://www.fda.gov/opacom/7alerts.html>).

#### *D. Other Comments on Written Procedures*

(Comment 9) One comment stresses the need for flexibility in requiring written procedures, based on differences between individual activities and companies. The comment suggests companies should be required to review and determine the need for written procedures at each critical step of their operations and be prepared to defend those determinations as necessary.

(Response) To the extent the comment suggests we do not require any written procedures specific to a particular function or requirement, and allow firms to decide when and when not to include them, we disagree. We believe that written procedures for the specific operations we have identified should not be optional. We have no objection if firms decide to establish and follow additional written procedures, beyond those we require in this final rule. Although we require written procedures for entire subparts, or specific requirements within certain subparts, we provide flexibility for firms to establish those written procedures that will ensure the requirements are met.

(Comment 10) Some comments stress the importance of written procedures in enabling FDA to ensure compliance with the dietary supplement CGMP requirements.

(Response) We believe written procedures will help us to ensure compliance with these CGMP requirements because they will clearly communicate the steps the firm must take to satisfy the requirements. During an inspection, we observe the practices that employees follow. However, to ensure that a firm is consistently complying with CGMP requirements, our investigators need access to records that both describe a firm's processes and procedures and demonstrate whether the firm has been following them. Under the final rule, we require you to make and keep records of the written procedures in each applicable subpart. Such records would be available to us under the requirements of final subpart P, *Records and Recordkeeping*.

(Comment 11) Many comments object to FDA's stated reasons for not requiring written procedures for most activities, including concerns about cost control and burden reduction. The comments contend that written procedures actually save time and other resources because they greatly facilitate employee training and ensure that activities are performed consistently and correctly. Some comments assert most companies already have written procedures in place, so start-up costs associated with such requirements would be minimal. One comment notes written procedures would be among the least costly of all the procedural requirements proposed by FDA.

(Response) We agree that requiring that operations be conducted using written procedures can save time and other resources by facilitating employee training and ensuring operations are performed consistently and correctly. Because following written procedures can help ensure uniformity in the

process and ensure the quality of the dietary supplement at every step, periodic end product testing can be sufficient to determine whether your manufacturing process is controlled. CGMP is premised upon quality assurance at every step of the process. It is less costly to establish and follow written procedures than it would be to test each finished batch for conformance with specifications.

As suggested by these comments, our analysis (section XXIV of this document) shows that the overall costs are reduced, in part, because requiring that certain operations be conducted using written procedures enables us to reduce requirements for testing at the finished batch stage.

(Comment 12) One comment states training employees on the required hygienic practices prior to their first day of handling product is critical to ensuring product safety.

(Response) The requirement to establish and follow written procedures to fulfill the requirements of subpart B does not establish any fixed requirement for when an employee must receive such training relative to when the employee handles product. However, final § 111.12(c) requires that any person engaged in manufacturing, packaging, labeling, or holding, or in performing any quality control operations, must have the education, training, or experience to perform the person's assigned functions. We therefore assume that employees will have the necessary education, training, or experience for each operation that they perform before they perform it.

(Comment 13) Some comments make recommendations for what written procedures should contain, including general parameters that should be included in all written procedures and specific parameters that should be included in specific written procedures. The general parameters include identification of the company; title that reflects the activities to be performed;

identification or control number with a revision level code; effective date; the number of pages in the procedure (e.g., by a procedure such as listing page numbers using a convention such as “page 1 of 4”); approval date and signature(s); references to linked or related procedures or forms; definitions of technical terms and acronyms; list of equipment, materials, and supplies needed in performing the task; who has the responsibility for performing each task; when and where a task is to be performed; concise step-by-step instructions for performing the task; the expected results from performing the task; what data to collect; and how to analyze, file, or report the collected data. In the specific case of written procedures for cleaning equipment and utensils, some comments suggest the written procedures include descriptions of appropriate cleaning agents, methods of cleaning, and the intervals and schedules for cleaning equipment.

(Response) We agree the suggestions provided by these comments are useful to include in any written procedures. However, to provide the flexibility necessary to address diverse dietary supplement manufacturing processes, we are leaving details such as these to the judgment of the company rather than prescribing them within the final rule.

(Comment 14) Some comments request the final rule include requirements for managing changes to written procedures. One comment states changes to written procedures should be reviewed, justified, documented, approved, and implemented in a defined manner. The comments explain that “Change control procedures” define what is and what is not covered by the written procedure and how proposed changes will be identified or recommended, processed, reviewed, and approved.

(Response) As discussed in final subpart F, the final rule requires that quality control personnel approve all written procedures. “All” written procedures includes revisions to written procedures. As discussed in this section, the final rule requires you to establish and follow written procedures for quality control operations. We believe that procedures for managing changes to written procedures can be addressed within the written procedures for quality control operations.

(Comment 15) Some comments assert the final rule should not require written procedures for key operations because the rule should stay focused on end results and not process.

(Response) We disagree. The essence of good manufacturing practice that is established by this final rule is a production and process control system that is designed to ensure the quality of the dietary supplement.

#### *E. What Other General Comments Did We Receive?*

(Comment 16) Some comments say any final rule should not require written procedures, should not propose a definition of appropriate tests, and generally should not include requirements for procedures better left to “normal business practices.” The comments cited Executive Order 12866 and the Small Business Regulatory Enforcement Flexibility Act (SBREFA). The comment added that there is no such requirement in the food CGMPs or in the 1997 ANPRM.

(Response) We disagree the final rule violates either Executive Order 12866 or SBREFA and discuss this in section XXIV of this document. We address SBREFA’s regulatory flexibility issues by staggering compliance dates so that certain businesses would have 24 and 36 months, respectively, to comply with the final rule. As for the assertion that food CGMPs do not require

written procedures, we discuss the requirements of food CGMPS in relation to the requirements of these dietary supplement CGMPs in section V of this document. The comment's assertion that the 1997 ANPRM did not contain written procedures is incorrect. The industry draft that we published in the 1997 ANPRM had multiple written procedures, including written procedures for:

- Cleaning and maintaining equipment and utensils used in the manufacture of products;
- The receipt, identification, examination, handling, sampling, testing, and approval or rejection of raw materials;
- Appropriate tests and/or examinations to be conducted to assure the purity, composition, and quality of the finished product;
- The method for reprocessing batches or operational start-up materials that do not conform to finished goods standards or specifications;
- The control procedures employed for the receipt, storage, handling, sampling, examination, and/or testing that may be necessary to assure the identity of labeling and the appropriate identity, cleanliness, and quality characteristics of packaging materials for dietary products;
- Ensuring correct labels, labeling, and packaging materials are issued and used for dietary products; and
- Describing the handling of all written and oral complaints regarding a product.

(62 FR 5700 at 5704 through 5706).

(Comment 17) In the analysis of impacts in the 2003 CGMP Proposal (68 FR 12157 at 12222), we stated that we had considered imposing fewer CGMP requirements for the manufacture of vitamins and minerals. Although this

issue arose as a discussion of regulatory options that we had considered and rejected, we received several comments on this subject. Some comments state we should not create different CGMP standards based upon the type of dietary ingredient. These comments state that one set of appropriately flexible standards would be more efficient and less confusing to industry than separate standards for each portion of the industry. Some comments say that different requirements for vitamins and minerals would cause problems because most people who use these products take a multivitamin/mineral preparation as their primary and sole dietary supplement, so the risk of adverse events arising from adulteration, misidentification, or misformulation of products would be much higher if vitamins and minerals were subject to fewer requirements compared to other dietary supplements. Other comments supported the concept of differing standards. Some comments assert, in order for the CGMP regulations to set minimum quality standards for all dietary supplements, we would have to regulate each facet of the manufacture, packaging, and storage of a dietary supplement independently of product type. These comments state reducing the requirements for vitamin and mineral manufacturers would not allow the development of minimum quality standards across the entire dietary supplement industry.

(Response) The concept of fewer requirements for vitamins and minerals was simply one regulatory option we considered as part of the 2003 CGMP Proposal's analysis of impacts (see 68 FR 12157 at 12220 through 12223). We rejected it (*id.*). We disagree with the comments that there should be fewer CGMP requirements for vitamins and minerals. Neither the 2003 CGMP Proposal, nor this final rule, imposes fewer requirements on vitamin or mineral firms compared to firms that make other types of dietary supplements.

## V. What Legal Authority Comments Did We Receive?

Many comments were submitted from individuals, companies, and trade groups concerning our legal authority for this rule. Most of the comments question the scope of the rule based on the language in section 402(g) of the act (21 U.S.C. 342(g)) stating that “regulations shall be modeled after current good manufacturing practice regulations for food.” Other comments question our authority for records access. Some comments assert that certain provisions of the proposed rule are unconstitutionally vague, and therefore violate the Fifth Amendment. A few comments disagree with our rationale for why dietary supplements are different than conventional food and need separate CGMP requirements. We address these comments immediately below in this section.

### *A. Modeled After CGMP for Food*

(Comment 18) Some comments support our approach of proposing requirements that are more comprehensive than the CGMP requirements for food. One comment states that the current requirements for food CGMP are less comprehensive than the CGMP requirements in current use by both the food and dietary supplement industries and the current “best practices” should be incorporated into the dietary supplement CGMP rule. Several comments state that the requirements for dietary supplement CGMP do not need to be identical to the requirements in existing food CGMP regulations, that appropriate manufacturing controls are needed for dietary ingredients contained in dietary supplements to protect the public health, that some borrowing of drug CGMP concepts may be necessary, and that we should balance effective control with necessary flexibility in the dietary supplement CGMP rule. In addition, one comment states that the USP manufacturing

guidelines, which contain wording from the drug CGMP requirements, are a model for dietary supplement CGMP for many in industry.

Several comments express concern about not deviating too drastically from the requirements in existing food CGMP regulations. Although several comments recognize that additional CGMP provisions for dietary supplements, such as those related to identity, purity, strength, quality, and composition, are needed, the comments say that we should not regulate dietary supplement manufacturing in the same manner as drug manufacturing because it would entail overly burdensome methods for production and process controls. Some comments contend that some of the proposed rule requirements exceed the drug CGMP requirements.

Most of the comments assert that the proposed dietary supplement CGMP requirements are not modeled after the CGMP regulations for food. The reasons for this assertion vary. Some assert that certain provisions in the proposed rule were not found in, or differ from, the provisions in part 110. Examples of proposed requirements that comments indicate exceeded food CGMP included batch testing, packaging and labeling, recordkeeping, consumer complaints, and the use of validated methods. Other comments state that the proposed requirements exceeded those for food because the proposed rule provided for finished testing of certain substances when used as dietary supplements, such as garlic and ginger, whereas no such testing is required under existing food CGMP regulations when those same substances are used as conventional food. One comment says the rule was modeled after juice hazard analysis and critical control point (HACCP) and therefore goes beyond existing food CGMP regulations.

Some comments assert that the proposed requirements exceed the existing food CGMP regulations because certain proposed provisions contained a level of detail that is not in the food or the drug CGMP regulations, or because elements of a provision in the proposed rule were similar to a provision in part 210 (21 CFR part 210) (drug CGMP regulation). Other comments disagree with our rationale that the proposed rule was designed on the same principles as the existing food CGMP regulations to address the characteristics and hazards specific to dietary supplements, or to prevent adulteration in preparing, packaging, or holding dietary supplements. The comments also disagree that we may include provisions in the dietary supplement CGMP final rule that were not found in the food CGMP regulations at the time DSHEA was enacted.

Several comments state that we exceed our legal authority for the proposed rule because it used too broad a definition of “modeled after.” Some comments offer their own definitions of “model;” others object to the use of the noun form “model” and provide dictionary definitions of the verb form “modeled.” A few comments assert that the meaning of “model” is clear, despite different dictionary meanings, and that the statute is not ambiguous under *Chevron U.S.A. Inc. v. Natural Resources Defense Council*, 467 U.S. 837 (1984) (“*Chevron*”). One comment states that, even if the language is ambiguous and our interpretation merits deference, our interpretation is too expansive and not based on a permissible construction of the statute. Another comment states that we did not explain why our interpretation was consistent with our congressional mandate.

(Response) We agree with the comments stating that the dietary supplement CGMP requirements in this final rule need not be identical to the

existing food CGMP regulations and that a system of manufacturing controls specific to dietary supplements is needed. We do not agree that we exceeded the scope of our authority under section 402(g) of the act in issuing the proposed requirements for dietary supplement CGMP or these final requirements. Our interpretation of the language in section 402(g) of the act, including the “modeled after” language, as to what requirements of the act we have authority to issue, is based on a permissible construction of the statute.

The comments present the following general questions: (1) Whether the statute gives us authority to promulgate CGMP requirements for dietary supplements that are not identical to the requirements in existing CGMP regulations for food and (2) if so, whether the requirements in this final rule that differ from those in existing CGMP regulations for food are fairly encompassed within Congress’ direction that the dietary supplement regulations shall be “modeled after” food regulations and, therefore, are based on a permissible construction of the statute.

Under section 402(g)(1) of the act, a dietary supplement is deemed to be adulterated if it has “been prepared, packed, or held under conditions that do not meet current good manufacturing practice regulations, including regulations requiring, when necessary, expiration date labeling, issued by the Secretary under subparagraph (2).” Section 402(g)(2) of the act authorizes the Secretary, by regulation, to “prescribe good manufacturing practices for dietary supplements.” Congress further provided that such regulations “shall be modeled after current good manufacturing practice regulations for food” and “may not impose standards for which there is no current and generally available analytical methodology.”

In construing the meaning of section 402(g) of the act, and, in particular, the language in that section stating that such regulations shall be “modeled after current good manufacturing practice regulations for food,” we are confronted with two questions. First, has Congress directly and unambiguously spoken to the precise question at issue? (“*Chevron* step one”) (see *Chevron*, 467 U.S. at 842.) To find no ambiguity, Congress must have clearly manifested its intention with respect to the particular issue (see *Young v. Community Nutrition Institute*, 476 U.S. 974, 980 (1986)). If Congress has spoken directly and plainly, we must implement Congress’s unambiguously expressed intent (see *Chevron*, 467 U.S. at 842–843). Second, if the act is silent or ambiguous with respect to a particular issue in section 402(g) of the act, is our interpretation based on a permissible construction of the statute (“*Chevron* step two”) (*Chevron*, 467 U.S. at 843; *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 132 (2000))? When Congress leaves a gap for the agency to fill by regulation, the regulation will pass muster so long as it is not “arbitrary, capricious, or manifestly contrary to the statute” (*Chevron*, 467 U.S. at 843–844).

We believe that the language in section 402(g) of the act provides an express delegation of authority to us to promulgate a regulation to “prescribe good manufacturing practices for dietary supplements” so long as those regulations are “modeled after the current good manufacturing practice regulations for food.” The express language in section 402(g) of the act contemplates broad, but not unlimited, agency discretion as to what to include in a dietary supplement CGMP regulation.

Congress has also spoken to the precise question of whether the dietary supplement CGMP requirements must be identical to the requirements in

existing food CGMP regulations. If Congress had wanted dietary supplement CGMP to be identical to food CGMP, it easily could have required that by statute. Indeed, if Congress had intended for CGMPs for dietary supplements to be the same as food CGMPs, there would have been no need for Congress to have addressed the issue at all; as a type of food, dietary supplements would otherwise be governed by the food CGMPs. See section (ff) of the act (21 U.S.C. 321(ff)). Instead, the statute calls for us to issue regulations that are “modeled after” CGMP regulations for food. The plain meaning of a “model” or “modeled after,” as discussed in the 2003 CGMP Proposal (68 FR 12157 at 12165) and in the comments, relates to a pattern, plan, representation, or simulation. The use of the term “modeled after” makes it clear that the regulations need not be identical to the original, but instead are contemplated to differ from the original.

Thus, the additional, independent authority to promulgate CGMP regulations for dietary supplements that Congress provided in section 402(g) of the act, without delineating what requirements such a regulation could or could not include, left us with considerable authority to fill in the gaps in ways that recognize the differences between dietary supplements and other foods that warrant different manufacturing controls. A contrary interpretation, as some comments suggested, that the “modeled after” language means the requirements for dietary supplement CGMP must be precisely found in current part 110, or other food CGMP regulations, would so narrowly circumscribe our discretion as to make it impossible to tailor the regulation to fit the products it is designed to address. Such an interpretation would lead to a rule that would “frustrate the success of the regulation undertaken by Congress” because it would not take into consideration the characteristics, hazards, and

manufacturing practices specific to dietary supplements (*American Trucking Ass'ns v. U.S.*, 344 U.S. 298, 311 (1953)).<sup>4</sup>

Congress has also spoken to the precise question of which requirements CGMP “regulations for food.” The plain meaning of “*regulations*” is plural (more than one), and the plain meaning of “*food*” is as Congress defined in section 201(f) of the act, including articles “used for food or drink.” At the time DSHEA was enacted, there were five food CGMP regulations: Those for infant formula (part 106), thermally processed low-acid canned food (part 113), acidified food (part 114), bottled water (part 129), and general food (part 110, often referred to as the “umbrella” regulations). All of these regulations appear in Subchapter B of Chapter 1 of Title 21 of the Code of Federal Regulations, entitled “Food for Human Consumption.” Nothing in the language of section 402(g) or elsewhere suggests that Congress meant to limit the term CGMP “regulations for food” to only the regulation in part 110. Thus, it is consistent with our statutory authority for us to look to all of our food CGMP regulations—including infant formula, low-acid canned foods, acidified foods, and bottled water, as well as our general food CGMP regulations—after which to model our dietary supplement CGMP regulations.

Congress has not spoken to the precise question of what specific requirements for dietary supplements may be imposed under the “shall be modeled after” language. Given this ambiguity, therefore, under *Chevron* step two, we may determine what requirements to include in this final rule for

---

<sup>4</sup>The Senate Report on DSHEA states that Congress inserted section 402(g) because it recognized that “dietary supplements may require different manufacturing and quality controls” when compared to food CGMP (S. Rep. No. 140, 103rd Cong., 2d Sess., at 31 (1994)). However, the report is not considered legislative history. Congress issued a Statement of Agreement (140 Cong. Rec. S14801 (Oct. 7, 1994), reprinted in 1994 U.S.C.C.A.N. 3523) that stated “it is the intent of the chief sponsors of the bill \* \* \* that no other reports or statements be considered as legislative history for the bill”).

dietary supplement CGMP, provided that our interpretation is not arbitrary, capricious, or manifestly contrary to the statute (*Chevron*, 467 U.S. at 844).

Accordingly, we considered the types of requirements in the existing food CGMP regulations and used those as models for the dietary supplement CGMP requirements. We considered both the objectives and the means of achieving the objectives in the existing food CGMP regulations. These CGMP food regulations include those for infant formula (part 106), general food (“umbrella” regulations) (part 110), thermally processed low-acid canned food (part 113), acidified food (part 114), and bottled water (part 129). Each of these food CGMP regulations provides objectives and means upon which we modeled the dietary supplement CGMP regulations. Just as the precise requirements of the other food CGMP regulations are tailored to the particular characteristics and hazards of the foods and manufacturing processes being addressed, the dietary supplement CGMP requirements are also so tailored.

For example, the infant formula CGMP regulation is intended to ensure that the “safety and nutritional potency” of a formula are “built into the manufacturing process” in order to establish a quality control system to make sure that infant formula products are properly manufactured (47 FR 17016 at 17017, April 20, 1982). The specific criteria in the regulations apply in determining whether the infant formula meets the safety, quality, and nutrient requirements of the act (§ 106.1(a)). The means to achieving the objectives in the infant formula regulations include, for example, requirements for ingredient control (through a supplier’s guarantee or certification or through analysis of the ingredient) (§ 106.20); preparation of a master manufacturing order and a system to assure and verify the addition of each ingredient (§ 106.25); either in-process batch testing (§ 106.25(b)) or sampling and testing

of each batch to ensure nutrient requirements are met (§ 106.30); and coding to enable ready identification of lots during their sale and distribution (§ 106.90).

The infant formula CGMP regulation also includes numerous requirements that manufacturers maintain records, e.g., records on certain food-packaging materials; records on nutrient premix testing; certificate and guarantees from premix suppliers for required nutrients; records of results of testing conducted by suppliers; records of tests to establish the purity of each nutrient, the weight, and amounts of nutrients; records to ensure proper nutrient quality control; records to ensure required nutrient control at the final product stage; distribution records; records on microbiological quality and purity of raw materials; and records of audits (§ 106.100). The infant formula CGMP regulation also requires manufacturers to maintain procedures describing how complaints will be handled, to follow those procedures, and to investigate when a complaint shows a possible health hazard (§ 106.100(k)). Quality control records must contain enough information to permit a public health evaluation of any batch of infant formula (§ 106.100(o)). All required records must be available for authorized inspection (§ 106.100(l)).

Many provisions of the dietary supplement CGMP final rule are similar in objective and means and are “modeled after” the provisions of the infant formula CGMP regulation. For example, like the infant formula regulation, the dietary supplement CGMP regulation is designed to establish a quality control system to make sure that dietary supplements are properly manufactured. The dietary supplement regulation uses similar means to ensure this goal, such as requirements for ingredient control (through supplier’s certificate of analysis or testing or examination) (final § 111.75(a)); preparation of a master

manufacturing record (final § 111.205); in-process batch monitoring (final § 111.75(b)) or batch testing or examination (final § 111.75(c)); and coding to provide a batch, lot, or control number (final § 111.260(a)). Like the infant formula CGMP regulations, the dietary supplement CGMP final rule contains recordkeeping requirements related to packaging materials; certificates of analysis from suppliers; results of tests that you conduct, for example, on ingredients or the finished batch; and results of chemical, microbiological, or other tests that you conduct as necessary to prevent the use of contaminated components (final §§ 111.95, 111.180(b)(2), 111.260(h), 111.325(b)(2), and 111.365(d)). Also similar to the infant formula CGMP regulation, the dietary supplement CGMP final rule requires manufacturers to maintain procedures for handling complaints (final §§ 111.553 and 111.570(b)(1)); to investigate certain complaints (final § 111.560(a)(2)); and to keep records of complaints (final § 111.570(b)(2)). Required dietary supplement records must also, as with infant formula records, be available for inspection by FDA (final § 111.610(a)).

The “umbrella” food CGMP regulation in part 110 details practices to ensure “(1) that food is manufactured, processed, packed, and held under conditions that are sanitary, and (2) that such food is safe, clean, and wholesome” (44 FR 33238 at 33239, June 8, 1979). Promulgated primarily under the adulteration provisions of section 402(a)(3) and (a)(4) of the act, as well as section 361 of the Public Health Service Act (the PHS Act) (42 U.S.C. 264), the umbrella CGMP food regulation requires a quality control operation whose main purpose is “to provide a systematic procedure for taking all actions necessary to prevent food from being adulterated within the meaning of the act” (51 FR 22458 at 22461, June 19, 1986), as well as to prevent the spread of food-borne communicable diseases (44 FR 33239, June 8, 1979) (see

§ 110.5(a)). Part 110 also “specifies requirements that must be met to produce safe and wholesome food” (51 FR 22461). These umbrella food CGMP requirements not only pertain to food safety, but also are “concerned with contamination by filth or decomposition which may or may not raise safety concerns” (51 FR 22458 at 22462).

The detailed requirements of the umbrella food CGMP regulation accomplish these objectives through a variety of means. For example, there are specific personnel provisions requiring employees who may be sources of microbial contamination to be excluded from certain operations (§ 110.10(a)); persons working in contact with food, food-contact surfaces, and food-packaging materials to follow hygienic practices (§ 110.10(b)); and that certain personnel have sufficient education or experience to produce clean and safe food (§ 110.10(c)). The umbrella food CGMP regulation also includes detailed requirements concerning the grounds surrounding a food plant and the design of buildings and structures to protect against contamination or to maintain sanitary operations and produce safe food (§ 110.20). Detailed provisions also require that physical facilities be maintained in sanitary condition and in sufficient repair to prevent food from being adulterated (§ 110.35). Any water that contacts food or food-contact surfaces must be “safe and of adequate sanitary quality” (§ 110.37(a)); plumbing, sewage, and other disposal, as well as toilet facilities, must also protect against contamination (§ 110.37(b), (c), and (d)). Similarly, equipment and utensils must be designed and maintained to preclude adulteration and food contact surfaces must be maintained to protect food from being contaminated by any source, including unlawful indirect food additives (§ 110.40(a)). All operations for receiving, inspecting, transporting, segregating, preparing, manufacturing, packaging, and storing food must be

conducted using adequate sanitation principles (§ 110.80). Appropriate quality control operations must be used to ensure that food is suitable for human consumption and that food-packaging materials are safe and suitable (§ 110.80). Foods must be stored and transported under conditions to protect against physical, chemical, and microbial contamination, as well as against deterioration of the food and the container (§ 110.93).

The provisions of the umbrella food CGMP regulation serve as the model for many dietary supplement CGMP provisions. For example, the dietary supplement CGMP requirements concerning personnel and microbial contamination (final § 111.10(a)); hygienic practices (final § 111.10(b)); and education, training, or experience (final § 111.12) are very similar to provisions in part 110. In addition, the dietary supplement CGMP requirements concerning the grounds, physical plant facilities, cleaning materials, pest control, water supply, plumbing, sewage disposal, bathrooms, and trash disposal (final §§ 111.15 and 111.20) closely resemble the analogous part 110 requirements.

Because of the particular hazards associated with low-acid canned foods and with acidified foods, the CGMP regulations for these foods contain detailed provisions to ensure safe manufacturing. Specifically, the CGMP regulations for these foods protect the public health against microbial contamination from these foods. Part 113 sets out safe manufacturing, processing, and packaging procedures for low-acid foods in hermetically sealed containers. The CGMP criteria in this part apply in determining whether the facilities, methods, practices, and controls used by commercial processors of such foods are operated “in a manner adequate to protect the public health” (§ 113.5). Processors of low-acid canned foods must have a “scheduled process” that is