USP Compounding Standards

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Healthcare Quality Standards
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USP's Beginning

1820

Spalding

Bigelow

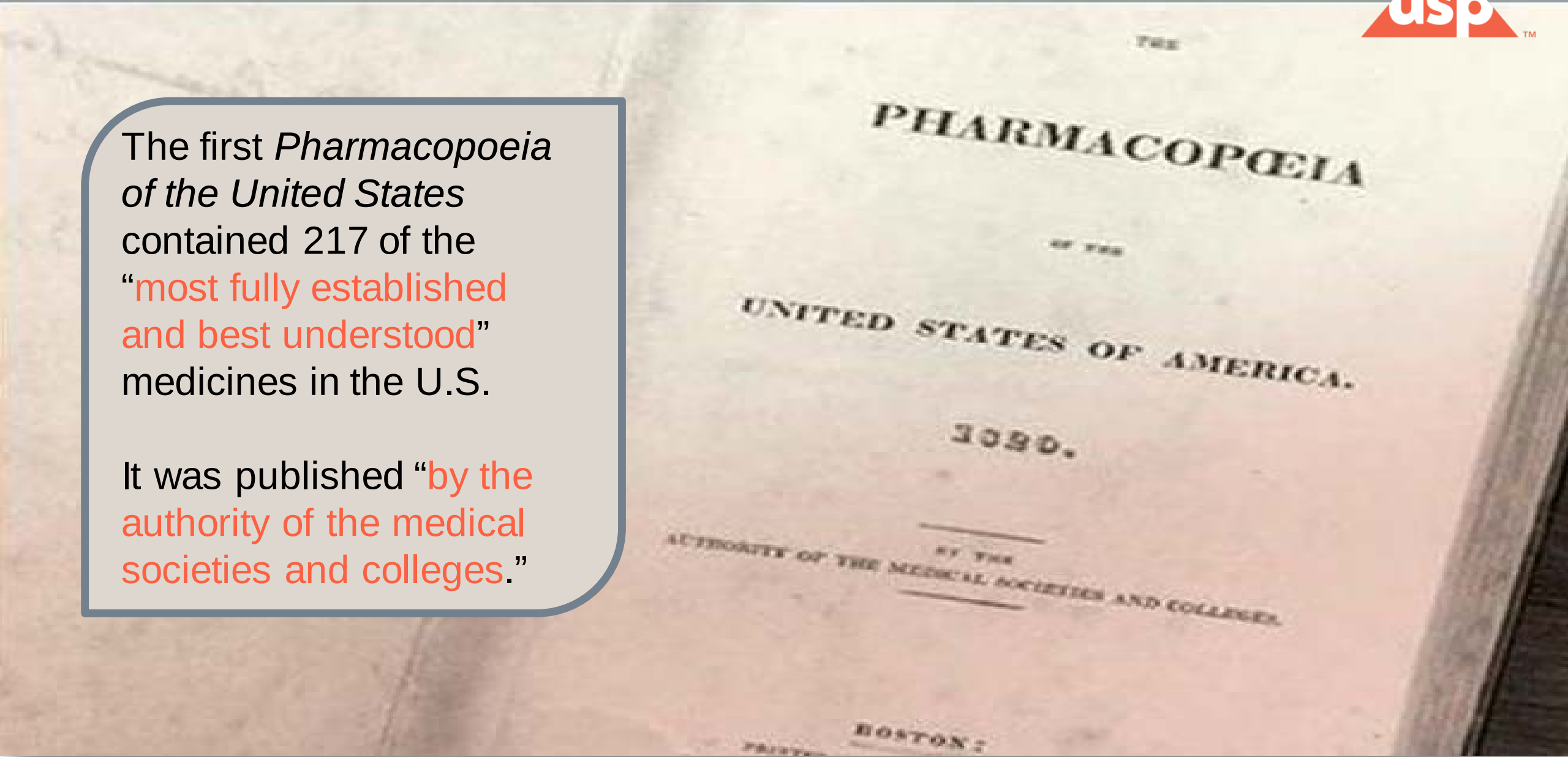
Mitchill

USP was founded in 1820 by
11 physicians, in Washington, D.C.

The First Pharmacopeia (1820)

The first *Pharmacopoeia of the United States* contained 217 of the "most fully established and best understood" medicines in the U.S.

It was published "by the authority of the medical societies and colleges."



Objective

*"It is the object of a Pharmacopeia to **select** from among substances which **possess medicinal power**, those, the utility of which is m**ost fully established and best understood**; and to **form from them preparations** and compositions, in which their **powers may be exerted to the greatest advantage**. It should likewise distinguish those articles by convenient and definite names, such as may prevent trouble or uncertainty in the intercourse of physicians and apothecaries."*

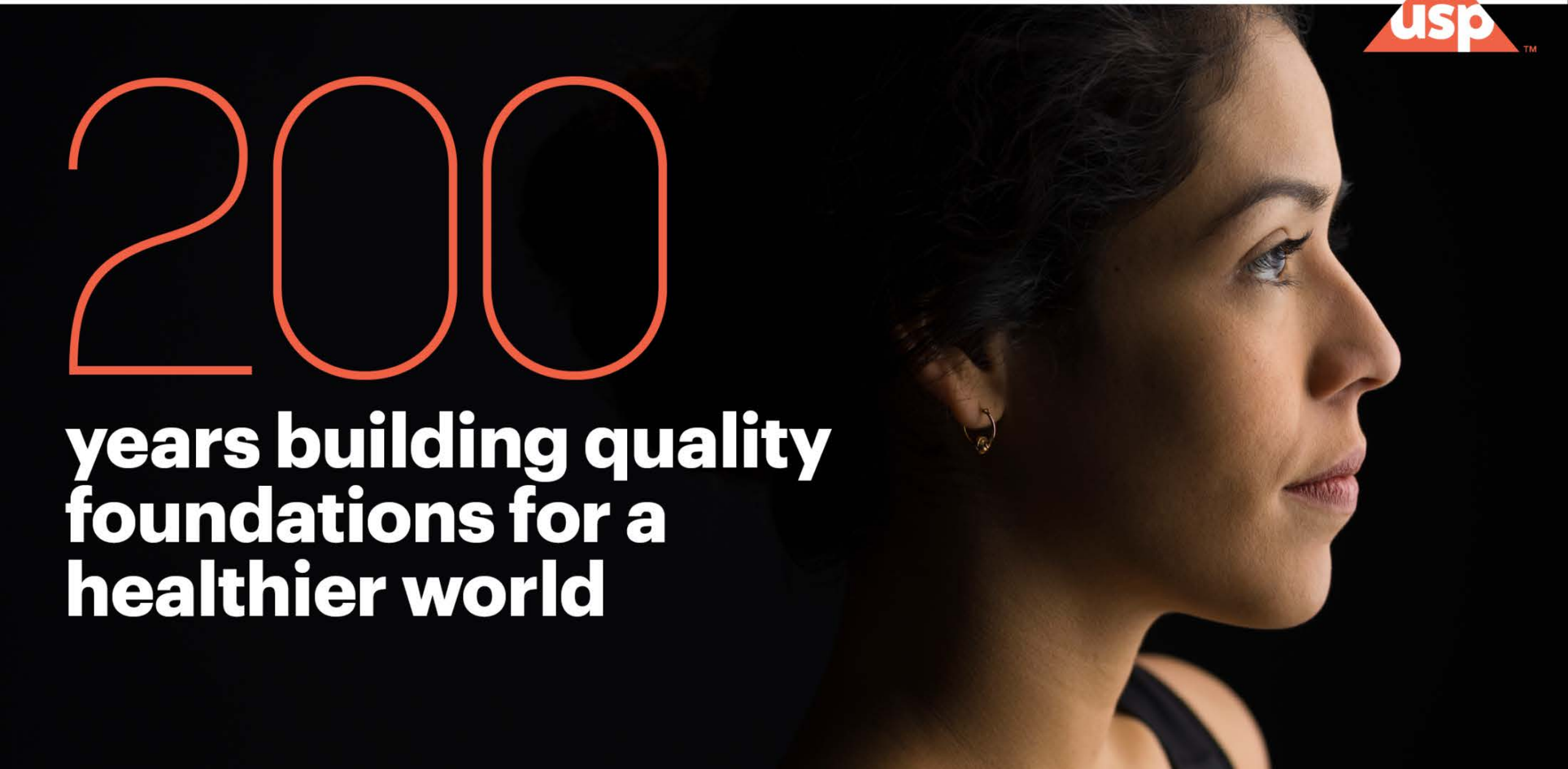
Physicians

Preface – USP 1820

Pharmacists

Patients

Who We Are

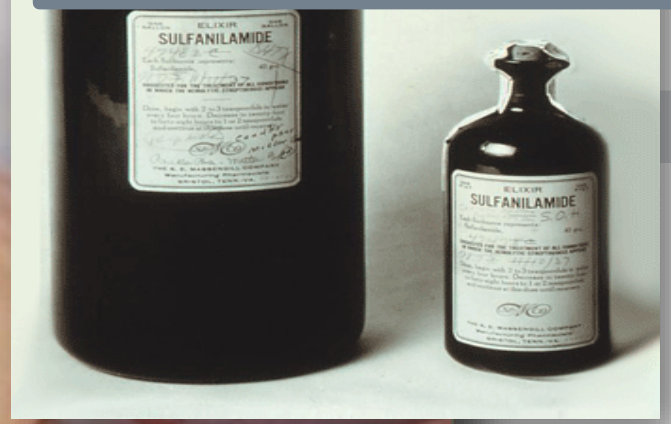

usp
200
years building quality
foundations for a
healthier world

Legal Recognition

The requirements of the Federal Food Drug and Cosmetic Act apply equally to drugs that are compounded and those that are manufactured….

2013 Drug Quality & Security Act

Recognized USP monographs for bulk substances



The experts behind our standards

The experts behind our standards

2015–2020 Council of Experts

Healthcare Quality Standards Collaborative Group

- Nomenclature & Labeling
- Compounding
- Healthcare Quality

Chemical Medicines Monographs Collaborative Group

- Chemical Medicines Monographs 1
- Chemical Medicines Monographs 2
- Chemical Medicines Monographs 3
- Chemical Medicines Monographs 4
- Chemical Medicines Monographs 5
- Chemical Medicines Monographs 6

Biologics Collaborative Group

- B101 Peptides
- B102 Proteins
- B103 Complex Biologicals
- BIO4 Antibiotics
- GC Biological Analysis

Excipient Monographs Collaborative Group

- Excipient Monographs 1
- Excipient Monographs 2

Dietary Supplements/ Herbal Medicines/Foods Collaborative Group

- Non-Botanical Dietary Supplements
- Botanical Dietary Supplements & Herbal Medicines
- Food Ingredients

General Chapters Collaborative Group

- Chemical Analysis
- Physical Analysis
- Statistics
- Microbiology
- Dosage Forms
- Packaging & Distribution

How we work

Stakeholders

USP actively seeks engagement with stakeholders throughout the standard-setting process through stakeholder meetings, advisory roundtables, and open-microphone webinars.

- Healthcare Practitioners
- Patients
- Academicians
- Healthcare Industry
- Regulatory Authorities
- Manufacturers

USP Process

1. Public Health Need

- Need identified by any stakeholder or USP
- Need evaluated for possible standard development

2. Draft Standard

- Best practices and scientific information collected

3. Public Comment Period

- Draft standard published for stakeholder input

4. Review & Approval

- Comments evaluated and addressed <or> Comments evaluated and further revision and comment needed

Revision Continues

Approved

5. Publication

- Final standard published with official date at least 6 months after publication

USP Expert Committee

USP convenes a committee of independent experts that are knowledgeable on the public health issue to develop the standard.

- Healthcare Practitioners
- Academicians
- Healthcare Industry
- Regulatory Authorities (Non-voting Liaisons)
- Manufacturers

Stakeholder Implementation

Regulatory Authorities, State Practice Boards, Healthcare Industry, Healthcare Practitioners and other stakeholders utilize USP Healthcare Quality & Safety standards within their specific authority to help ensure public health.

Types of USP Compounding Standards

There are 3 types of standards for compounding:

1. Monographs for ingredients used in compounded preparations
   - Drug Substance Monographs
2. Monographs for compounded preparations
   - Compounded Preparation Monographs
3. Practice standards
   - General Chapters

⟨797⟩ PHARMACEUTICAL COMPOUNDING–STERILE PREPARATIONS

INTRODUCTION

The objective of this chapter is to describe conditions and practices to prevent harm, including death, to patients that could result from (1) microbial contamination (nonsterility), (2) excessive bacterial endotoxins, (3) variability in the intended strength of correct ingredients that exceeds either monograph limits for official articles (see "official" and "article" in the *General Notices and Requirements*) or 10% for nonofficial articles, (4) unintended chemical and physical contaminants, and (5) ingredients of inappropriate quality in compounded sterile preparations (CSPs). Contaminated CSPs are potentially most hazardous to patients when administered into body cavities, central nervous and vascular systems, eyes, and joints, and when used as baths for live organs and tissues. When CSPs contain excessive bacterial endotoxins (see *Bacterial Endotoxins Test* ⟨85⟩), they are potentially most hazardous to patients when administered into the central nervous system.

Compounding Chapters Overview

General Chapters can be:

- **Compendially applicable**
  - Numbered below <1000> and referenced in General Notices, a monograph, or another applicable general chapter below <1000>
- **Informational**
  - Numbered between <1000> and <1999>
- **Specific for dietary supplements**
  - Numbered above <2000>

Terminology

- "**Shall**" OR "**Must**" requirements
- "**Should**" recommendations

USP Compounding General Chapters

- **Practice Standards**
  - <795> *Pharmaceutical Compounding – Nonsterile Preparations*
  - <797> *Pharmaceutical Compounding – Sterile Preparations*
  - <800> *Hazardous Drugs – Handling in Healthcare Settings*
  - <1163> *Quality Assurance in Pharmaceutical Compounding*
  - <1160> *Pharmaceutical Calculations in Prescription Compounding*
  - <1176> *Prescription Balances & Volumetric Apparatus*
  - <1168> *Compounding for Phase I Investigational Studies (Official Mar – 01 – 2019)*

BUD Provisions in <795>: Pharmaceutical Compounding – Nonsterile preparations

Default BUDs

- Water containing oral formulations = **14 days**
- Water-containing topical/dermal and mucosal liquids and semisolid = **30 days**
- Nonaqueous formulations = **6 months**

General guidelines for assigning Beyond-Use Dates

- Compounders shall consult drug-specific and general stability documentation and literature when available and should consider:
  - the nature of the drug and its degradation mechanism
  - the dosage form and its components
  - the potential for microbial proliferation in the preparation
  - the container in which it is packaged
  - the expected storage conditions
  - the intended duration of therapy

BUD Provisions in <797>: Pharmaceutical Compounding – Sterile Preparations

Default BUDs

- Low-risk in Segregated Compounding area
  - 12 hours at controlled room temperature
- Low-risk (in cleanroom suite)
  - 48 hours at controlled room temperature
  - 14 days in a refrigerator
  - 45 days in a freezer
- Medium-risk (in a cleanroom suite)
  - 30 hours at controlled room temperature
  - 9 days in a refrigerator
  - 45 days in a freezer
- High-risk (in a cleanroom suite)
  - 24 hours controlled room temperature
  - 3 days refrigerator
  - 45 days frozen

Single-dose containers

Opened in ISO Class 5 air	Worse than ISO Class 5 air
6 hours	1 hour

Multiple-dose containers

- 28 days

Compounded Preparation Monographs

Metronidazole Benzoate Compounded Oral Suspension

DEFINITION

Metronidazole Benzoate Compounded Oral Suspension contains NLT 90.0% and NMT 110.0% of the labeled amount of metronidazole ($C_6H_9N_3O_3$).

Prepare Metronidazole Benzoate Compounded Oral Suspension containing 50 mg/mL of metronidazole as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩).

Metronidazole (as the Benzoate) powder	5 g (8 g)
Ora-Blend[a], a sufficient quantity to make	100 mL

[a] Perrigo, Minneapolis, MN.

Place the *Metronidazole Benzoate powder* into a suitable mortar. Wet the powder with a small amount of *Ora-Blend*, and triturate to make a smooth paste. Add the *Ora-Blend* in small portions almost to volume, and mix thoroughly after each addition. Transfer the contents of the mortar, stepwise and quantitatively, to a calibrated container. Add sufficient *Ora-Blend* to bring the preparation to final volume. Shake to mix well.

ASSAY

- **Procedure**

Solution A: 0.1% (v/v) glacial acetic acid in water

Mobile phase: Acetonitrile and *Solution A* (40:60). Filter, and degas.

Standard solution: 0.4 mg/mL of metronidazole prepared from USP Metronidazole Benzoate RS in *Mobile phase*. Mix well until dissolved.

Sample solution: Shake thoroughly each bottle of Oral Suspension. Transfer 0.8 mL of the Oral Suspension into a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix well.

Chromatographic system

(See *Chromatography* ⟨621⟩, *System Suitability*.)

Mode: LC

Detector: UV 316 nm

Column: 4.6-mm × 15-cm; 5-µm packing L1

Column temperature: 30°

Flow rate: 1.0 mL/min

Injection volume: 5 µL

System suitability

Sample: *Standard solution*

[NOTE—The retention time for metronidazole is about 7.7 min.]

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0% for replicate injections

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of metronidazole ($C_6H_9N_3O_3$) in the portion of Oral Suspension taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of metronidazole in the *Standard solution* (mg/mL)
C_U = nominal concentration of metronidazole in the *Sample solution* (mg/mL)

SPECIFIC TESTS

- **pH** ⟨791⟩: 3.6–4.6

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Package in tight, light-resistant containers. Store at 2°–8° or at controlled room temperature.
- **Beyond-Use Date:** NMT 90 days after the date on which it was compounded when stored at 2°–8° or controlled room temperature.
- **Labeling:** Label it to indicate that it is to be well-shaken before use, and to state the *Beyond-Use Date*.
- **USP Reference Standards** ⟨11⟩

USP Metronidazole Benzoate RS

Metronidazole Capsules

DEFINITION

Metronidazole Capsules contain NLT 90.0% and NMT 110.0% of the labeled amount of metronidazole ($C_6H_9N_3O_3$).

IDENTIFICATION

- **A. Infrared Absorption** ⟨197K⟩

Wavelength range: Between 1600 and 1000 cm^{-1}

Acceptance criteria: Capsule contents show maxima only at the same wavelengths as those of similarly prepared USP Metronidazole RS.

- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

- **Procedure**

Mobile phase: Methanol and water (1:4)

Standard solution: 0.03 mg/mL of USP Metronidazole RS in *Mobile phase*

Sample stock solution: Nominally 1 mg/mL of metronidazole prepared as follows. Mix the contents of Capsules (NLT 20). Transfer an amount equivalent to 100 mg of metronidazole to a 100-mL volumetric flask, add 80 mL of *Mobile phase*, and sonicate with intermittent shaking for 10 min. Shake for 30 min, and dilute with *Mobile phase* to volume. Centrifuge a portion of the solution.

Sample solution: 0.03 mg/mL of metronidazole in *Mobile phase*, from the *Sample stock solution*. Pass a portion of the solution through a nylon membrane filter of 0.45-µm or finer pore size. Discard the first 10 mL of the filtrate, and use the remainder.

Chromatographic system

(See *Chromatography* ⟨621⟩, *System Suitability*.)

Mode: LC

Detector: UV 319 nm

Column: 4.6-mm × 15-cm; 5-µm packing L7

Column temperature: 30°

Flow rate: 1 mL/min

Injection volume: 30 µL

Run time: 2 times the retention time of the metronidazole peak

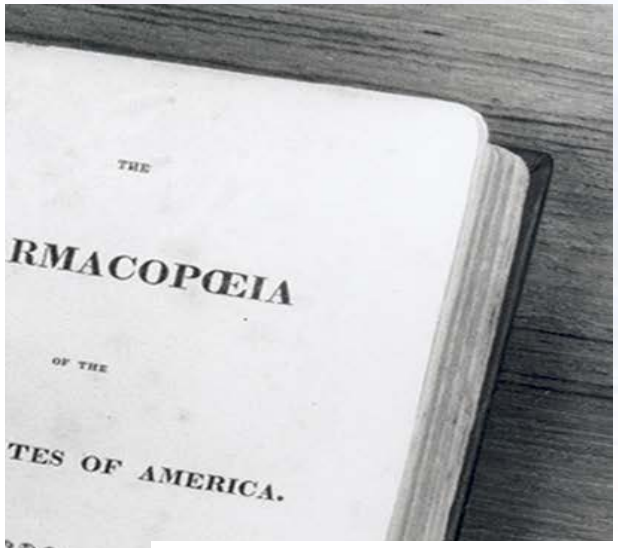
System suitability

Sample: *Standard solution*

Suitability requirements

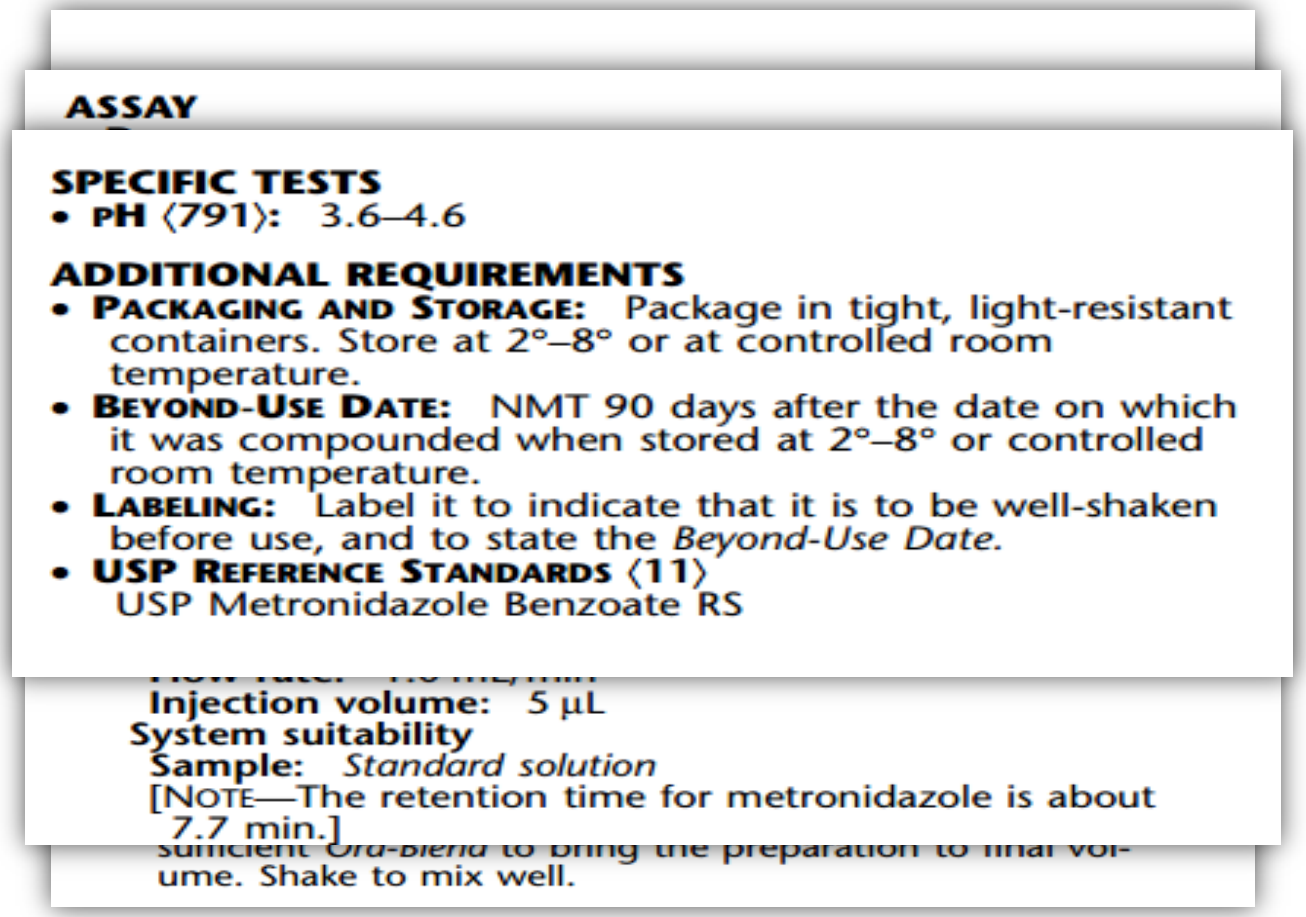
Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0% for five replicate injections



Components of a Compounded Preparation Monograph

- **Title**
- **Definition**
  - Lists the range of labeled amount of active ingredient
- **Formula**
  - Ingredients and quantities
- **Compounding Procedures**
- **Stability-indicating Assay**
- **pH**
- **Packaging and Storage**
- **Labeling**
- **Beyond-use dates**
  - Stability studies
  - General Chapters <795> or <797>



ASSAY

SPECIFIC TESTS
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ADDITIONAL REQUIREMENTS
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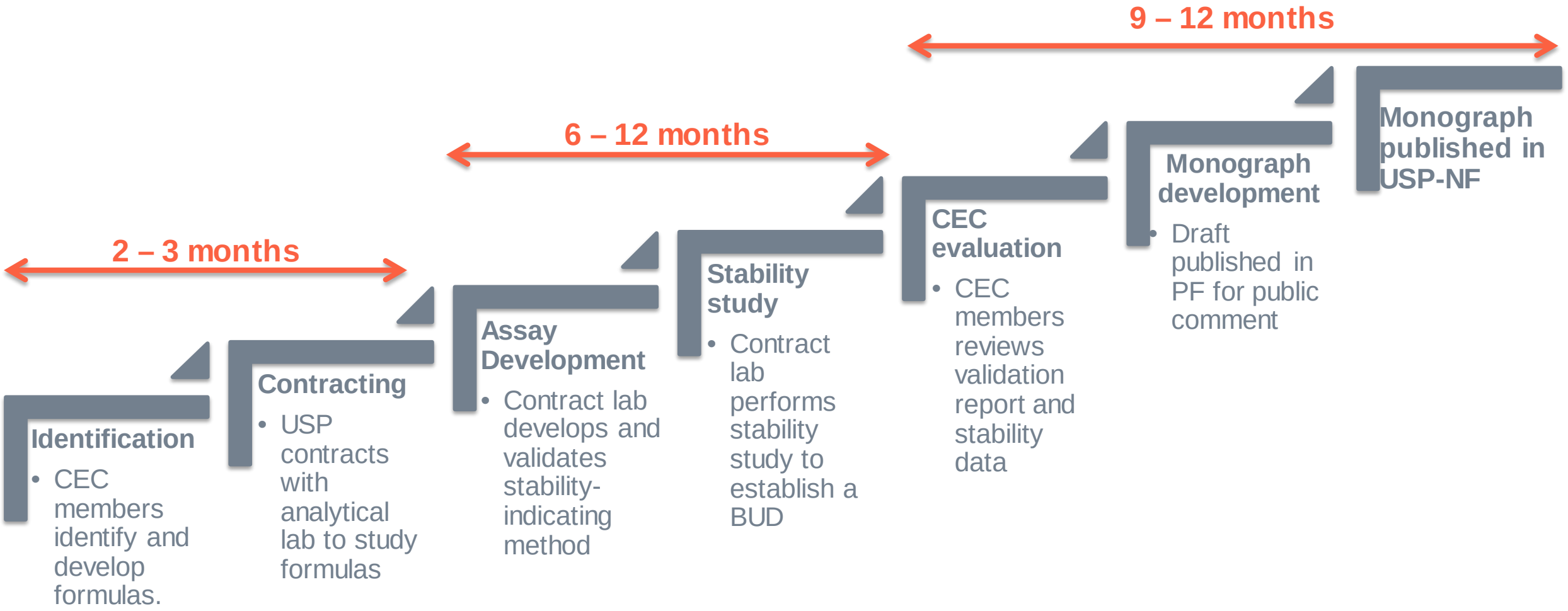
- **Labeling:** Label it to indicate that it is to be well-shaken before use, and to state the *Beyond-Use Date*.
- **USP Reference Standards** ⟨11⟩
  USP Metronidazole Benzoate RS

Injection volume: 5 µL
System suitability
Sample: *Standard solution*
[Note—The retention time for metronidazole is about 7.7 min.]
sufficient *Ora-Blend* to bring the preparation to final volume. Shake to mix well.

Current Compounded Preparation Monograph Development Process

Contract Laboratories



CPMs in the USP–NF

- Currently about 200
- 10 – 15 are added each year
- Suggested by members of Compounding Expert Committee
- Funded exclusively by USP

Challenges with current process:

- High cost
- Ever growing and changing public health needs

Compounded Preparation Monograph Donation program aims to accelerate this process through donations

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Thank You

Empowering a healthy tomorrow