USP Compounding Standards

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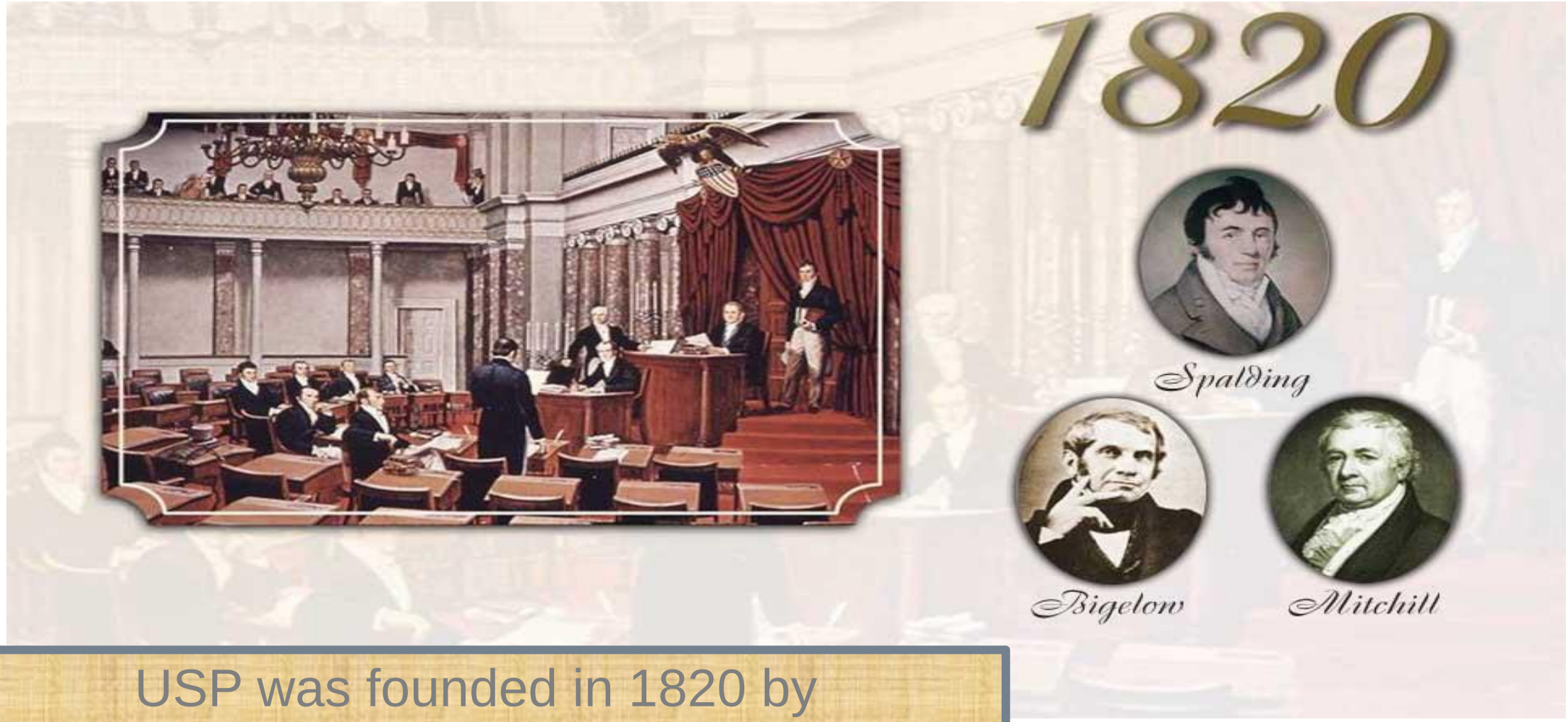
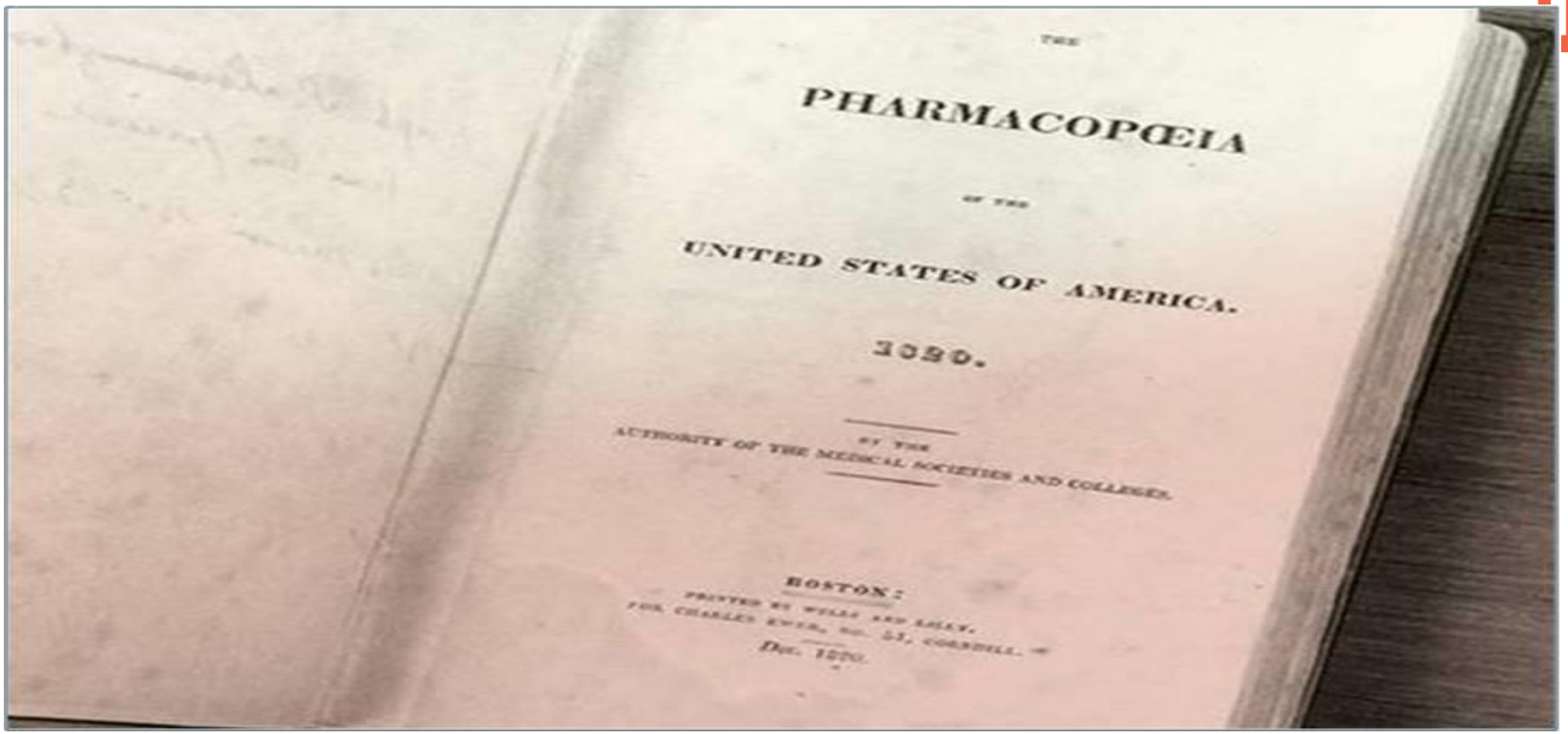
Healthcare Quality Standards

USP's Beginning



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 **most 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."*

Preface – USP 1820

What is Compounding ?

Definition

– The preparation, mixing, assembling, altering, packaging, and labeling of a drug, drug-delivery device, or device in accordance with a licensed practitioner's prescription, medication order, or initiative based on the practitioner/pharmacist/compounder relationship in the course of professional practice. (USP <795>)

Why compound?

– Pediatric patients
– Geriatric patients
– Animal patients
– Non-standard doses
– Allergen-free medication
– HRT
– Sports Injuries
– Pain management
– Access to critical medicines during shortages
– Discontinuation by manufacturer

Viable Alternatives?

– Crushing Tablets
– Powder Packets
– Splitting Tablets
– IV Solutions

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Compounding facilities

Section 503A and 503B of the FD&C Act

‘503A compounders’

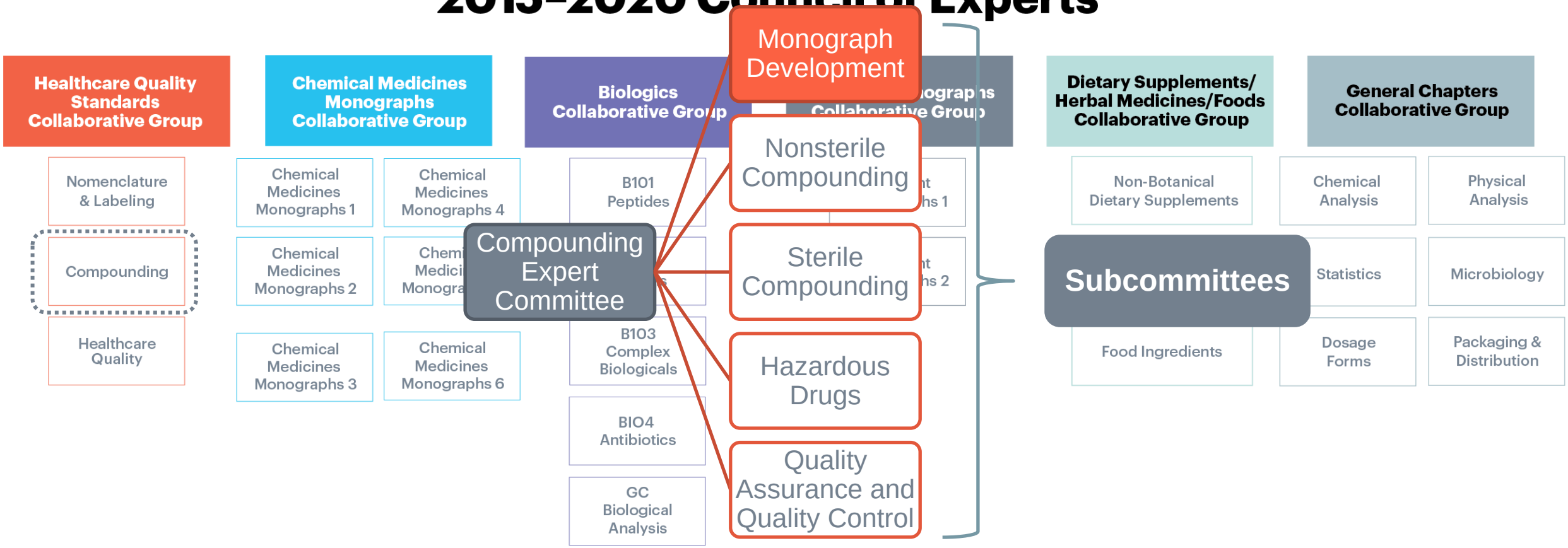
- Require a prescription
- Regulated by State Boards
- State laws and applicable USP standards (e.g. USP chapters)

‘503B compounders’

- Can compound with or without a Rx
- Outsourcing facilities (Can compound in bulk for dispensing to hospitals and for office use)
- Comply with 21 CFR Part 210 and 211 (cGMP)
- Must comply with state pharmacy laws AND are regulated by FDA

The experts behind our standards

2015–2020 Council of Experts



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.

2015 – 2020 Compounding Expert Committee

Chair: Gigi Davidson, B.S. Pharm, DICVP, NC State College of Veterinary Medicine
Vice Chair: Alan Parr, Pharm.D., Ph.D. BioCeutics, LLC

Member	Affiliation
Lisa Ashworth, B.S. Pharm	Children's Health System of Texas
Gus Bassani, Pharm.D.	PCCA
Edmund Elder, Ph.D. , B.S. Pharm	University of Wisconsin-Madison
Ryan Forrey, Pharm.D., M.S.	Beckon Dickinson
Deborah Houston, Pharm.D.	Novant Health - Kernersville Medical Center
Brenda Jensen, M.A.	Compounding Consultants, LLC.
Patricia Kienle, MPA, B.S. Pharm	Cardinal Health

2015 – 2020 Compounding Expert Committee

Chair: Gigi Davidson, B.S. Pharm, DICVP, NC State College of Veterinary Medicine
Vice Chair: Alan Parr, Pharm.D., Ph.D. BioCeutics, LLC

Member	Affiliation
William Mixon, B.S. Pharm	The Compounding Pharmacy
John Musil, Pharm.D.	Avella, Inc
David Newton, Ph.D.	Shenandoah University (retired)
Abby Roth, B.Sc.	ClinicalIQ
Robert Shrewsbury, Ph.D.	UNC Eshelman School of Pharmacy
Connie Rae Sullivan, B.S. Pharm	National Home Infusion Association
James Wagner	Controlled Environment Consulting
Brenda Yuzdepski, B.S. Pharm	Saskatoon Medical Arts Pharmacy

Public quality standards for compounded preparations

There are 3 types of standards for compounding:

- Monographs for ingredients used in compounded preparations
  - USP–NF Drug Substance Monographs
- Monographs for compounded preparations
  - Compounded Preparation Monographs
- Practice standards
  - General Chapters (e.g., <795> and <797>)

⟨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.

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*
- **New Standard**
  - <1168> *Compounding for Phase I Investigational Studies (Official on Mar 01, 2019)*

Component selection, handling and storage

Sample highlights from <795> and <797>

Responsibilities of the compounder include the following:

- Ingredients used in the formulation have their expected identity, quality, and purity.
- A *United States Pharmacopeia* (*USP*), *National Formulary* (*NF*), or *Food Chemicals Codex* (*FCC*) substance is the recommended source of ingredients for compounding all preparations.
- Use components manufactured in an FDA-registered facility.
- Official compounded preparations are prepared from ingredients that meet requirements of the compendial monograph for those individual ingredients for which monographs are provided. These preparations may be labeled *USP* or *NF* as appropriate.

USP Timeline for General Chapter Revisions

Note: The current version of General Chapters <795> and <797> published in USP-NF are official.

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

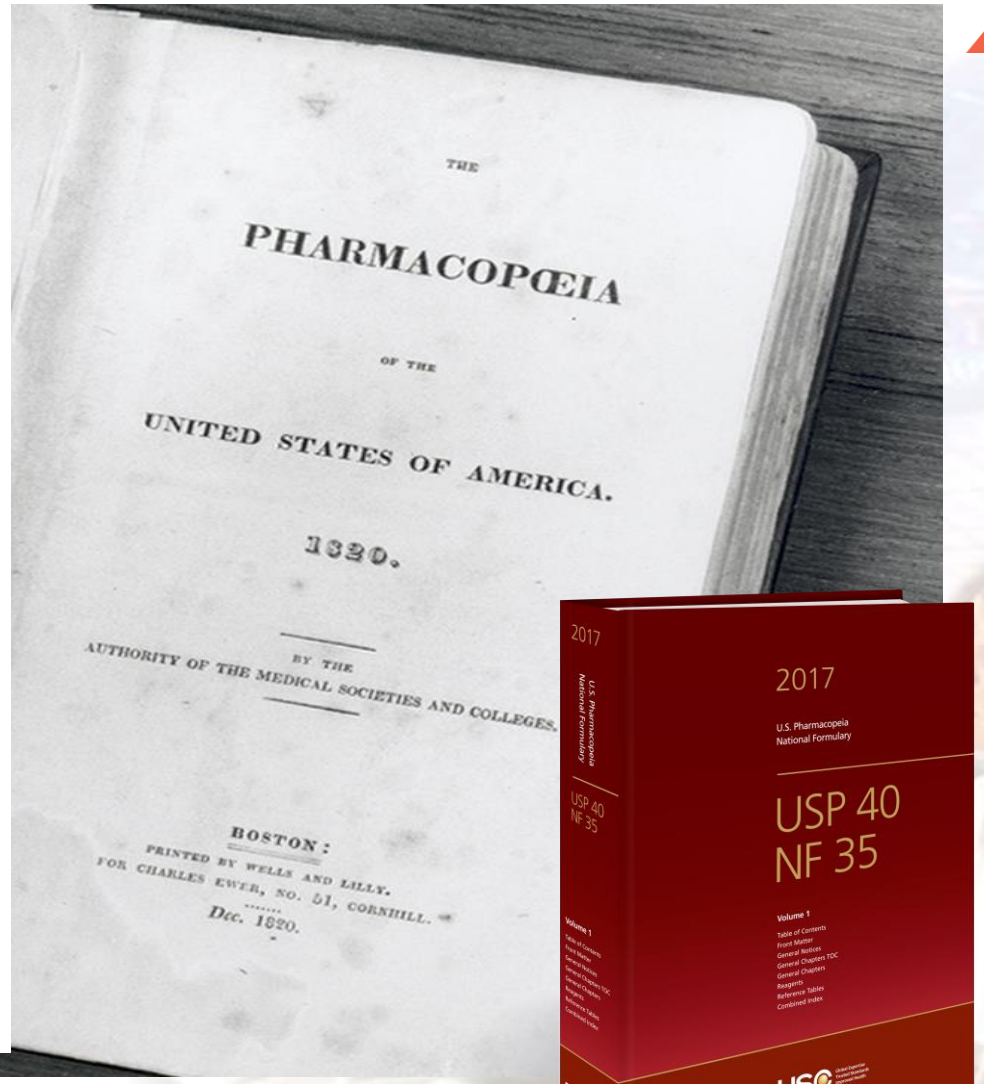
- **PROCEDURE**

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

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

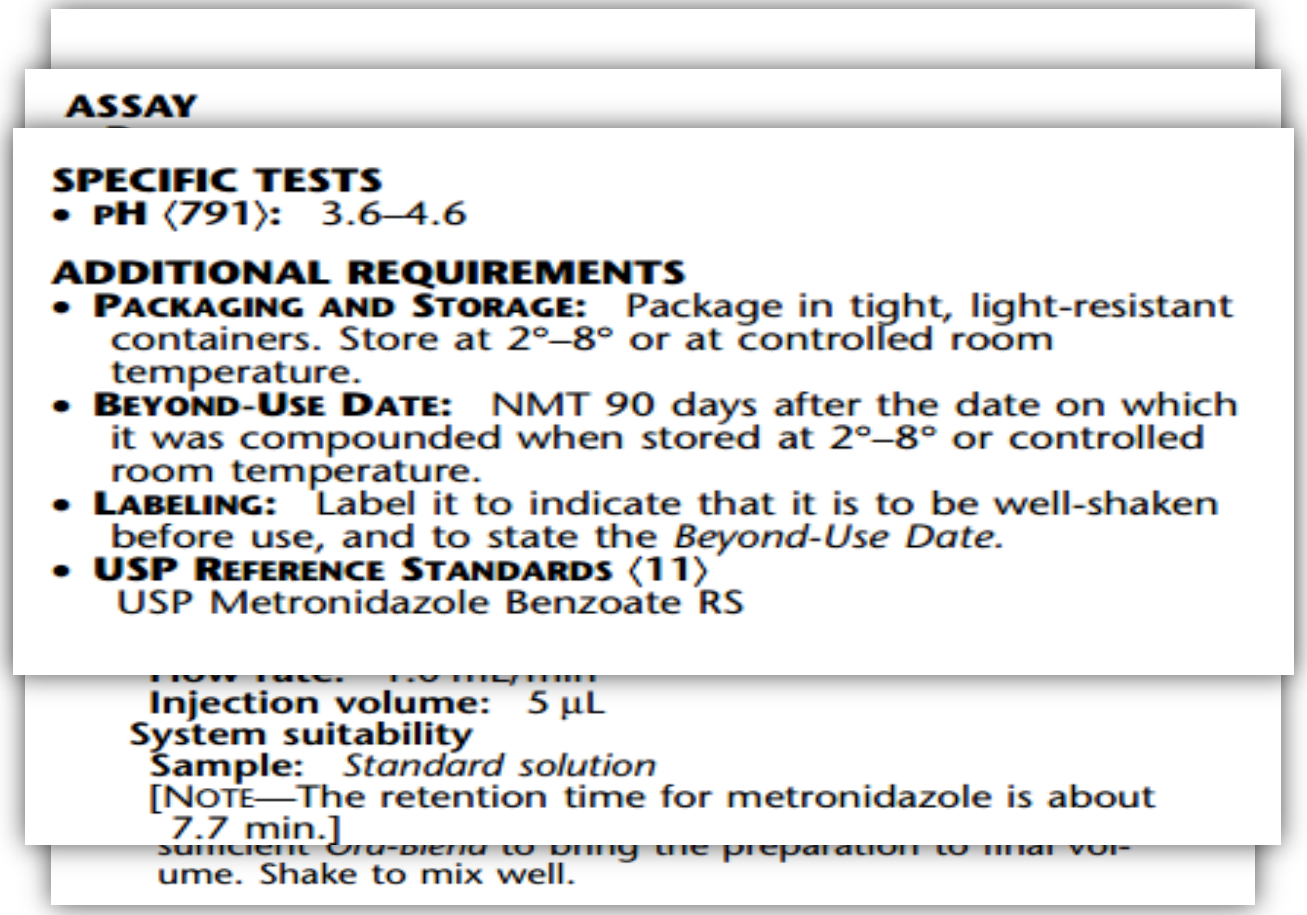
Standard solution: 0.4 mg/mL of metronidazole prepared from USP Metronidazole Benzoate RS in *Mobile phase*. Mix well until dissolved.

Sample solution: Shake thoroughly each bottle of Oral Suspension. Transfer 0.8 mL of the Oral Suspension into



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
- **pH** ⟨791⟩: 3.6–4.6

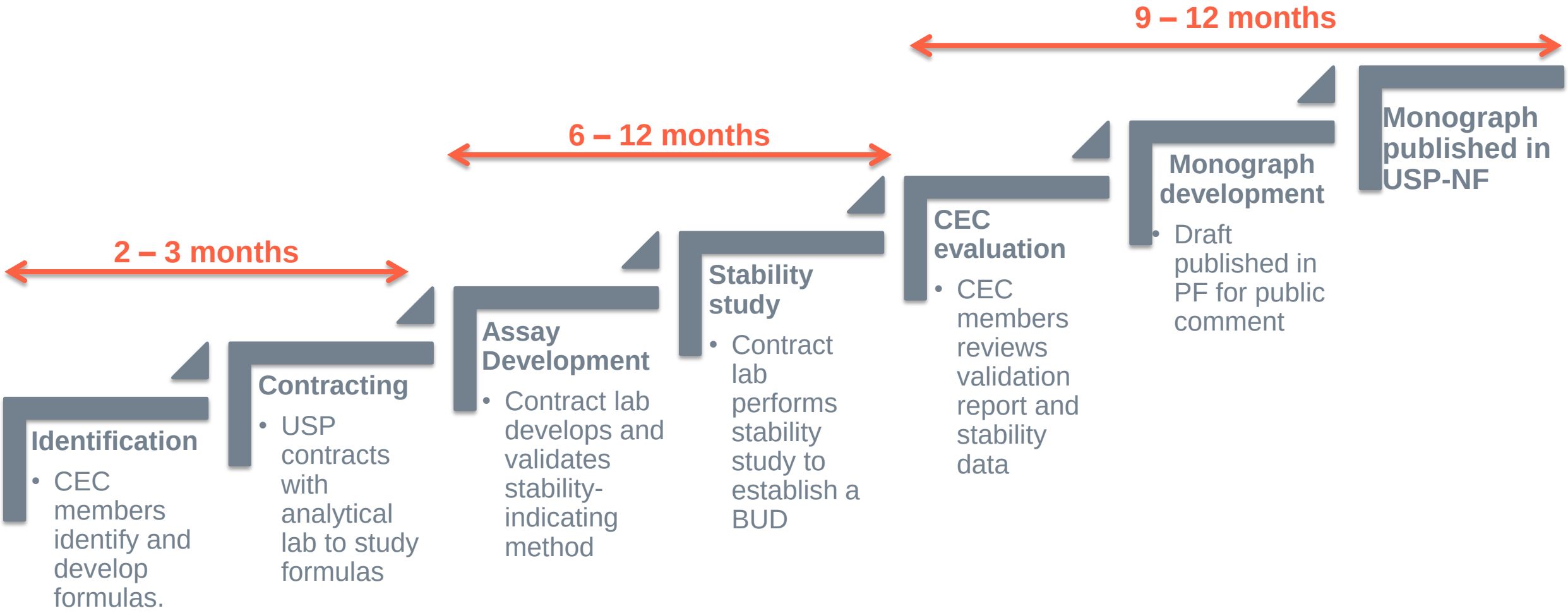
ADDITIONAL REQUIREMENTS
- **Packaging and Storage:** Package in tight, light-resistant containers. Store at 2°–8° or at controlled room temperature.
- **Beyond-Use Date:** NMT 90 days after the date on which it was compounded when stored at 2°–8° or controlled room temperature.
- **Labeling:** Label 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

Injection volume: 5 µL
System suitability
Sample: *Standard solution*
[Note—The retention time for metronidazole is about 7.7 min.]

ume. Shake to mix well.

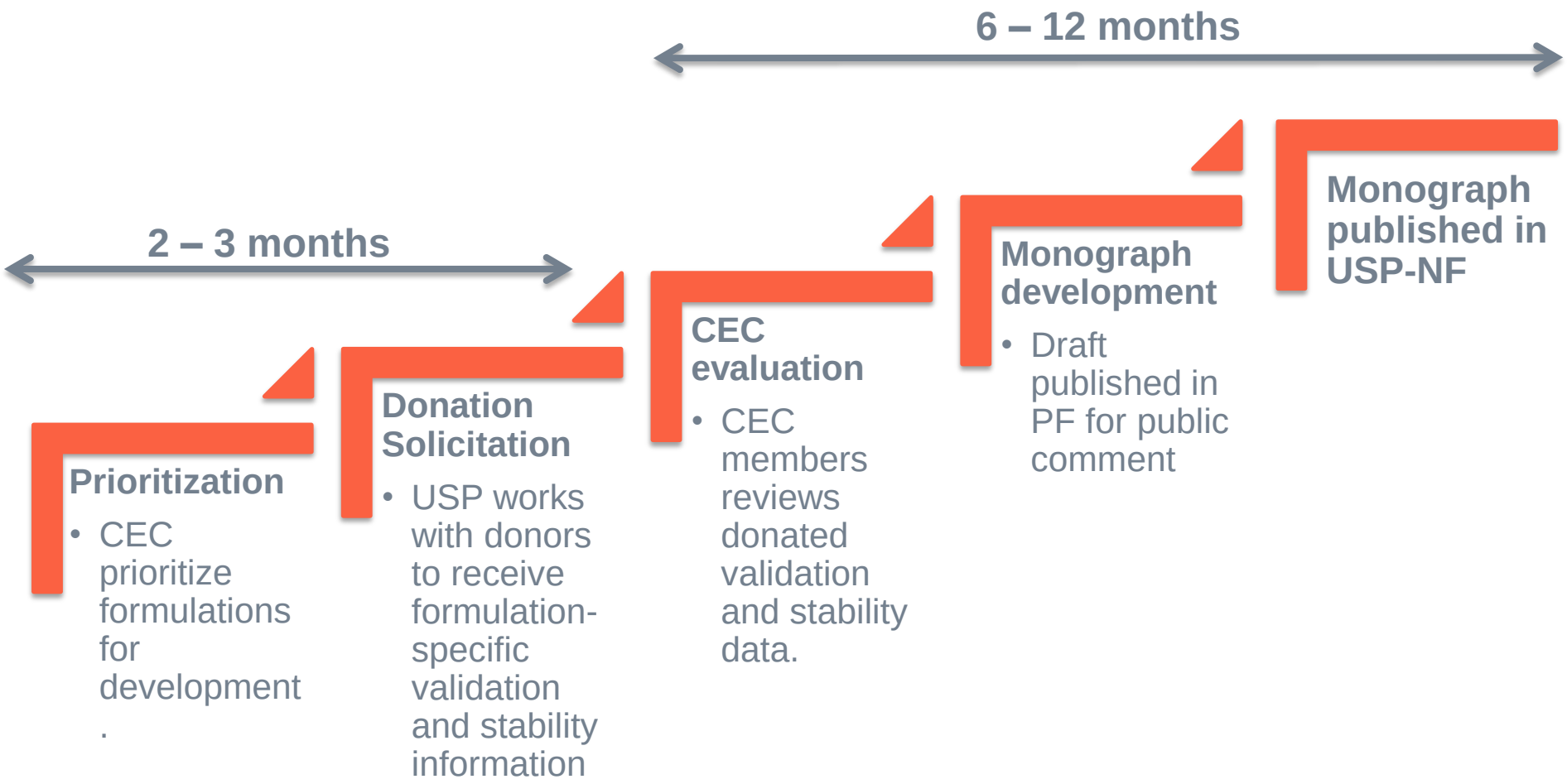
Current Compounded Preparation Monograph Development Process

Contract Laboratories



Current Compounded Preparation Monograph Development Process

Donation Program



Questions

Empowering a healthy tomorrow