CHAPTER 11

NON-STERILE AND STERILE MANUFACTURING

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Abstract

Pharmaceutical manufacturing encompasses both sterile and non-sterile preparation techniques required for specialized medication production beyond commercial availability. Non-sterile compounding transforms raw ingredients into patient-specific formulations including capsules, suspensions, ointments, and suppositories using pharmaceutical calculations ensuring accurate concentration, beyond-use dating based on stability data, and proper documentation meeting regulatory requirements including USP <795> standards and DQSA provisions. Sterile compounding applies aseptic techniques to prepare injections, ophthalmics, and other contamination-sensitive products, following USP <797> classifications of risk levels, environmental monitoring requirements, personnel qualification procedures, and beyond-use dating limitations that prevent microbiological or particulate contamination. Equipment and techniques for pharmaceutical preparation include electronic balances, ointment mills, powder blenders, laminar airflow workbenches, biological safety cabinets, and automated compounding devices, each requiring specific operation protocols, maintenance procedures, and performance verification to ensure accurate, consistent product generation. Quality assurance programs integrate environmental monitoring, personnel training, process validation, finished product testing, and comprehensive documentation systems that verify preparation integrity through particulate analysis, sterility testing, endotoxin evaluation, and potency assessment when applicable. These manufacturing principles enable pharmacies to face unmet medication needs through standardized processes that maintain product integrity, ensure patient safety, and fulfill regulatory obligations while providing therapy options unavailable through commercial channels.

Keywords: *Aseptic technique; Beyond-use dating; Environmental controls; Preparation validation; Regulatory compliance*

Learning Objectives

After completion of the chapter, the learners should be able to:

- Implement USP <795> standards for non-sterile compounding including appropriate garbing, documentation, and beyond-use dating determination.
- Apply aseptic technique principles following USP <797> guidelines for preparing sterile compounds across different risk levels.
- Operate specialized compounding equipment including electronic balances, laminar flow hoods, biological safety cabinets, and automated compounding devices.
- Design facility-appropriate environmental monitoring programs including viable and non-viable particle testing, surface sampling, and pressure differential verification.
- Develop comprehensive quality assurance protocols for both sterile and non-sterile preparations including process validation, personnel training, and end-product testing.
- Perform calculations necessary for preparing accurate compounded formulations including aliquoting, dilution, and concentration conversions.

NON-STERILE COMPOUNDING

Non-sterile compounding represents the art and science of creating customized medication preparations that are not required to be sterile. This practice addresses therapeutic needs unmet by commercially available products, including unique dosage forms, strengths, combinations, or formulations free from specific allergens or excipients. Non-sterile compounding requires thorough understanding of pharmaceutical principles including physical and chemical compatibility, stability considerations, and appropriate beyond-use dating to ensure both safety and efficacy of the final preparation.

Regulatory Guidelines and Standards

Non-sterile compounding operates within a comprehensive regulatory framework designed to ensure preparation quality and patient safety. The United States Pharmacopeia Chapter <795> establishes the foundational standards for non-sterile preparations, outlining requirements for facilities, equipment, personnel training, documentation, and quality control procedures. These standards classify compounded preparations based on complexity levels, with simple, moderate, and complex preparations requiring progressively more

rigorous controls. Regulatory oversight varies by jurisdiction, with state boards of pharmacy typically providing direct supervision of compounding pharmacies, while the Food and Drug Administration maintains federal authority, particularly regarding bulk drug substances and interstate distribution. The Drug Quality and Security Act of 2013 clarified the regulatory boundaries between traditional pharmacy compounding and larger-scale compounding operations functioning as outsourcing facilities. Documentation requirements include master formulation records detailing specific components, quantities, procedures, equipment, and quality control checks for each preparation. Compounding records document the actual preparation process for each batch, including component lot numbers, quantities used, preparation date, assigned beyond-use date, and personnel involved. Proper documentation supports quality assurance, regulatory compliance, and appropriate clinical use while enabling investigation of any quality or safety concerns that might arise. Training and competency assessment for compounding personnel must address not only technical skills but also understanding of underlying pharmaceutical principles, potential stability issues, and contamination prevention strategies appropriate to non-sterile operations.

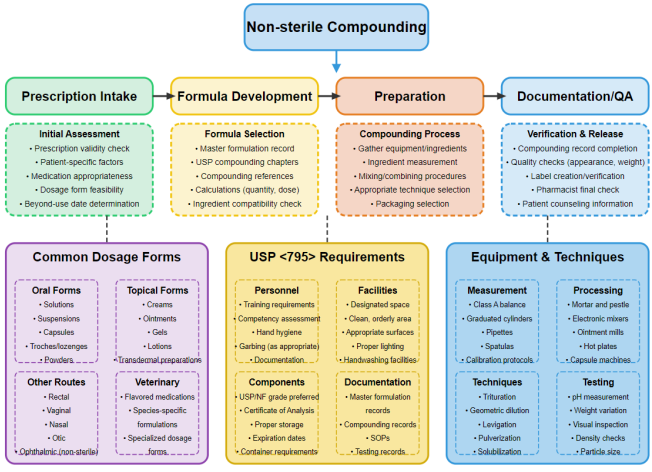

Figure 11.1: Non-sterile Compounding Process Flow

Table 11.1: Non-sterile Compounding Equipment and Uses

Equipment	Purpose	Cleaning/Maintenance
Electronic Balance	Accurate weighing of ingredients	Clean after each use Calibrate regularly Protect from dust Annual certification
Mortar and Pestle	Reducing particle size Mixing ingredients	Clean immediately after use Dedicate for specific uses Store dry
Spatulas	Transferring materials Mixing on ointment slabs	Clean after each use Inspect for damage Store properly
Graduated Cylinders	Measuring liquid volumes	Rinse immediately Dry inverted Inspect for chips/cracks
Ointment Mill	Reducing particle size in semisolids Creating homogeneous mixtures	Clean immediately Disassemble completely Lubricate moving parts
Ointment Slab	Mixing ointments and creams	Clean immediately Store protected Inspect for scratches
Pill Tiles	Mixing small quantities Capsule filling	Clean immediately Inspect for damage Store protected
Hot Plate/Magnetic Stirrer	Heating and mixing solutions	Clean after cooling Check electrical safety Calibrate temperature
Capsule Machines	Filling capsules uniformly	Clean thoroughly Store disassembled Check for damage
Suppository Molds	Forming suppositories	Clean immediately Store properly Check for damage

Equipment	Purpose	Cleaning/Maintenance
Electronic Homogenizer	Creating uniform suspensions/emulsions	Clean immediately Check electrical safety Inspect blades
Water Bath	Controlled heating	Regular water changes Check heating element Descale as needed
Unguator/Electronic Mortar and Pestle	Automated mixing of semisolids	Clean thoroughly Check electrical safety Maintain as directed

Formulation Development and Stability Considerations

Formulation development for compounded preparations requires systematic consideration of multiple pharmaceutical factors to ensure preparation stability, accuracy, and therapeutic efficacy. Vehicle selection significantly influences both physical and chemical stability while affecting palatability, administration ease, and potential excipient-related concerns. Aqueous vehicles provide appropriate matrices for water-soluble drugs but may promote hydrolysis of susceptible compounds. Non-aqueous vehicles including glycerin, propylene glycol, and fixed oils offer alternatives for water-sensitive medications but introduce different stability considerations. Chemical stability assessment considers potential degradation pathways including hydrolysis, oxidation, photolysis, and racemization. pH optimization represents a critical stability factor for many preparations, particularly those containing ionizable compounds with pH-dependent solubility and stability profiles. Buffer systems maintain pH within optimal ranges, preventing significant fluctuations that might compromise stability or therapeutic effect. Antioxidants including sodium metabisulfite, ascorbic acid, and butylated hydroxytoluene protect susceptible compounds from oxidative degradation, while chelating agents such as ethylenediaminetetraacetic acid (EDTA) bind trace metals that might otherwise catalyze oxidation reactions. Preservative selection addresses microbial contamination risk in multi-dose preparations, with systems including parabens, benzalkonium chloride, and potassium sorbate providing broad-spectrum activity when compatible with other formulation components. Beyond-use dating assignment follows systematic approaches outlined in USP <795>, considering water activity, pharmaceutical literature, stability-indicating analytical studies

when available, and appropriate safety factors. Conservative dating applies when limited stability data exists, while extended dating requires more substantial supporting evidence through published literature or formal stability studies.

Table 11.2: Non-sterile Compounding Bases and Vehicles

Base/Vehicle Type	Examples	Properties	Incompatibilities
Hydrophilic Ointment Bases	Polyethylene glycol ointment Aquaphor	Water-soluble/washable Absorbs water Minimal occlusion	Strong oxidizers Certain preservatives Incompatible with some ions
Hydrocarbon Bases	White petrolatum Yellow petrolatum Mineral oil	Occlusive Water-repellent Greasy feel	Water-soluble drugs High drug concentrations Hydrophilic substances
Absorption Bases	Hydrophilic petrolatum Lanolin Aquabase	W/O emulsion Some water absorption Occlusive properties	Some preservatives Highly charged molecules Extremes of pH
Water-Washable Bases	Hydrocream Vanishing cream Cetaphil	O/W emulsion Easy spreading Non-greasy	Oil-soluble drugs with poor solubility Substances affecting emulsion stability
Water-Soluble Bases	Polyethylene glycol Carbomer gels	Water-soluble Greaseless Washes off easily	Strong electrolytes Quaternary compounds Some preservatives

Base/Vehicle Type	Examples	Properties	Incompatibilities
Oral Solution Vehicles	Simple syrup Ora-Sweet Ora-Plus	Sweet taste Viscosity for suspension Preservative systems	Substances affecting pH Compounds incompatible with preservatives Oxidation-sensitive drugs
Suspending Agents	Methylcellulose Carboxymethylcellulose Xanthan gum	Increase viscosity Prevent settling Controlled flocculation	Strong electrolytes Extreme pH Certain preservatives
Suppository Bases	Cocoa butter Polyethylene glycol Witepsol	Melting/dissolving properties Drug release characteristics Physical stability	Water content >5% Substances affecting melting point Certain preservatives
Capsule Diluents	Lactose Microcrystalline cellulose Starch	Flow properties Compactibility Compatibility	Drugs that degrade lactose Moisture-sensitive drugs (with hygroscopic diluents) Incompatible drug-excipient combinations
Flavoring Agents	Fruit flavors Mint flavors Vanilla	Taste masking Patient acceptance Compatibility	Incompatible flavors pH-sensitive flavors Drug-flavor interactions
Sweetening Agents	Sucrose Saccharin	Improve palatability	Drug-sweetener