

QUALITY AND SAFETY IN COMPOUNDING NON-STERILE PREPARATIONS



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OVERVIEW

Patients are put at risk when compounded preparations are below regulatory standards. Multiple studies have shown pharmacy-compounded products (for example, bio-identical hormones, nitroglycerin ointments) are at risk for quality issues resulting in sub-potency, supra-potency, and even contamination.^{1,2,3} This article outlines important considerations when compounding non-sterile preparations by referring to the newly revised *United States Pharmacopeia (USP) Chapter <795> Pharmaceutical Compounding – Nonsterile Preparations (as of May 2011)* and the *Ontario College of Pharmacists (OCP) Guidelines for Compounding Preparations*. The USP <795> Chapter defines the specific criteria required to compound preparations of acceptable strength, quality, and purity with appropriate packaging and labeling in accordance with regulatory agencies. In Canada, drug manufacturing is regulated by Health Canada and compounding is an authorized act regulated by provincial authorities.⁴ The 2006 OCP Guidelines for Compounding Preparations (available at <http://www.ocpinfo.com> and currently under review) set standards for the quality and safety of compounding practices in Ontario pharmacies.⁵

The following section supports the preparation of non-sterile compounds within the context of USP specifications and provincial regulatory standards. Relevant medication incidents voluntarily reported to ISMP Canada (for instance, via the Community Pharmacy Incident Reporting (CPhIR) Program at <http://www.cphir.ca>) are used to highlight potential outcomes that may result when non-sterile compounding guidelines are not followed.

Before compounding a non-sterile preparation, the need for the compounded product is confirmed by checking for commercially available preparations in the Health Canada's Drug Product Database (<http://webprod3.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp>), and contacting manufacturers. To comply with the Health Canada policy on compounding, this confirmation is required in order to validate the lack of product availability and avoid duplicating an approved drug product.⁴

-1- PERSONNEL

After confirming the need to compound a preparation, designated managers need to ensure compounders (who are responsible for compounding preparations that are accurate and adhere to provincial standards) have accurate knowledge and expertise.⁵ The compounder must use professional judgement when deciding whether they have the expertise to compound a specific product.⁵ This includes understanding chemical and physical properties of ingredients, using appropriate equipment, and performing necessary calculations.⁵

-2- ENVIRONMENT

Compounders need to prepare non-sterile preparations in designated areas. Designated areas are described as an appropriate environment (i.e. adequate space, lighting, and storage) to prevent cross-contamination and the inadvertent addition of extraneous material to the medication.^{5,6} The OCP Guidelines for Compounding Preparations supports this practice by including provisions for sanitation.⁵ OCP recommends the pharmacy have a written sanitation program that specifies cleaning and disposal requirements.⁵ The written program should also address hygienic behaviors (such as, wardrobe, hand washing, management of injuries) of pharmacy staff engaging in compounding activities.⁵ Furthermore, the designated area should have access to potable water (i.e. drinking water) for hand and equipment washing.^{5,6}

-3- PROCEDURES AND RESOURCES

Sample Case 7: A pharmacist intended to compound an oral suspension of clonidine (using clonidine powder) for a 15-year-old male. The pharmacist incorrectly compounded the clonidine suspension (due to mixing up during calculations/conversions among grams, milligrams, and micrograms) resulting in a preparation 1,000 times more concentrated than prescribed. Before the error was discovered, the patient was admitted to hospital multiple times.

Designated managers need to provide compounders with necessary resources to consistently and accurately produce the intended preparation. Formulations should be accessed from a reputable source. If no formulation is available, a formula should be completed using knowledge in pharmacology, chemistry, and therapeutics.⁵ As seen in the *Sample Case* described above, a miscalculation led to dispensing a preparation

1,000 times more concentrated than the intended prescription.⁷ This incident emphasizes the importance of independent double checks and following standardized procedures to confirm accuracy and quality of compounded preparations. Along with defined policies and procedures, compounding preparations require the use of proper resources. This includes using equipment that is clean, and properly maintained.^{5,6} Compounding ingredients must be purchased from reliable sources that are of appropriate identity, quality, and purity.

Sample Case (from CPhIR): A male patient received a prescription for a 1% hydrocortisone in clotrimazole [cream]. The compounded preparation contained a piece of wax paper. The prescription was prepared from pre-made stock. The pharmacist did not notice the wax paper in the compounded product and the patient used the preparation containing the wax paper.

Quality control procedures are required to ensure accuracy and completeness.⁸ In the *Sample Case* described above, the pharmacy used pre-made stock to fill the prescription. Unfortunately, the pre-made stock contained wax paper that was included in the dispensed container. Although the wax paper did not cause harm to the patient, compounders are responsible for ensuring the final product appears as expected.⁸ If discrepancies are found in the final preparation, compounders need to resolve such discrepancies in preparation and/or appearance before dispensing to the patient.

-4- STABILITY ASSESSMENT

Sample Case (from CPhIR): A patient was prescribed sulfatrim oral suspension to be taken over a period of 90 days. A compounded oral suspension of sulfatrim is only stable for 20 days from its day of preparation.⁹ The pharmacist prepared and dispensed a 90 day supply of sulfatrim oral suspension. The medication error was caught during dispensing and the patient was given a 20-day supply with the remaining amount credited as refills.

As seen in the *Sample Case* described above, sulfatrim or co-trimoxazole oral suspension was not commercially available at the time of dispensing due to drug shortages, resulting in the need for the pharmacy to compound or prepare the oral formulation.⁹ The pharmacist in this particular near-miss situation almost dispensed a compounded preparation intended to be used past the acceptable beyond-use date. This illustrates the need for compounders to understand the concept of beyond-use dates.

What is the difference between expiry dates and beyond-use dates?

The manufacturer or distributor gives an *expiry date* to a drug product based on known stability data. It indicates the expected timeframe in which a drug product meets the therapeutic and stability requirements based on the published monograph or literature. *Beyond-use dates*, on the other hand, provide the date after which a compounded preparation shall not be used and are determined from the date when the preparation is compounded. Compounders provide the beyond-use date (based on the manufacturer's stability information and the literature with respect to stability, compatibility, and degradation of ingredients) to limit patient use of the compounded preparation. All compounded preparations must contain a beyond-use date.¹⁰

How do I figure out the beyond-use date for a compounded preparation?¹⁰

The beyond-use date is determined from the date of compounding by applying drug-specific and general stability resources, when available.¹⁰ These resources should consider the nature of the drug, degradation, packaging containers, storage conditions, and the duration of therapy.¹⁰ USP <795> states that when a manufactured product is used as an active ingredient in a compounded preparation, the product expiry date

cannot be used solely to assign a beyond-use date. Beyond-use dates should be assigned conservatively, while using professional judgment based on pharmaceutical education and experience. For non-sterile compounded preparations that are packaged in tight, light-resistant containers and stored at proper temperatures, consider the recommendations in Table 1 for beyond-use dates when established stability information is not available.¹¹ It is presumed that recommended beyond-use dates are for compounded preparations that are suitably preserved, where applicable, to protect against bacteria, yeast, and mould contamination.¹¹

Should consideration be given to the suitability of containers used for non-sterile compounded preparations?¹⁰

Sample Case: A child was prescribed an oral Prevacid® suspension. The pharmacist compounded the oral preparation and put it in a plastic amber bottle, instead of a glass amber bottle. Also, the mother was not aware that the oral preparation had to be refrigerated (no auxiliary label was placed on the prescription container) and [she] stored it at room temperature. The issues were resolved before the child took the medication.

Compounders are responsible for selecting the appropriate container for non-sterile compounded preparations.¹⁰ In the *Sample Case* described

TABLE 1: RECOMMENDED MAXIMUM BEYOND-USE DATES FOR NON-STERILE COMPOUNDED PREPARATIONS:¹¹

NON-STERILE PREPARATION	BEYOND-USE DATE
Non-aqueous Formulations (such as ointments, suppositories, troches, and others where no water is contained)	Not later than the time remaining until the earliest expiration date of any ingredient or 6 months, whichever is earlier
Water-containing Oral Formulations	Not later than 14 days for liquid preparations when stored at controlled cold temperatures (i.e. temperature thermostatically maintained between 2oC and 8oC)
Water-containing Topical/Dermal and Mucosal Liquid and Semisolid Formulations (such as preparations for topical application, like creams, gels, ointments, etc.)	Not later than 30 days

above, Prevacid® (lansoprazole) oral suspension was dispensed in a plastic amber bottle and no instructions were given to refrigerate the compounded medication. Plastic containers can contribute to decreased stability of some compounded products.¹² Ensom et al. showed oral lansoprazole preparations were stable for a longer period (91 days with or without refrigeration) in amber glass containers, compared to plastic containers (14 days when refrigerated).¹² This highlights the importance of using the correct container for non-sterile compounded preparation. Compounders are encouraged to review relevant resources before compounding and packaging non-sterile preparations.

IMPORTANT CONSIDERATIONS

Inappropriate compounding practices can put patients at risk for potentially harmful outcomes. Compounders unable to compound a drug product for the patient should refer the patient to a compounder with the ability to prepare the product.⁵ The references provided in this article can be used as a starting point to ensure quality and safety in the preparation of compounded products. Compounding ingredients (i.e. active pharmaceutical ingredients and excipients) have defined chemical and physical properties that are published in manufacturer monographs. However, the compounding process can change ingredient properties resulting

in altered quality, stability, and potency. These changes are highly dependent on the compounding formulation (i.e. capsules, solutions, ointments, etc.). It is vital for compounders to understand the impact of these alterations on the final product before patients are dispensed the compounded preparations. ■

The information in this article is adapted from the newly revised 2011 USP Chapter <795> Pharmaceutical Compounding – Nonsterile Preparations (which has incorporated USP Chapter <1075> Good Compounding Practices)¹⁰ and the 2006 Ontario College of Pharmacists (OCP) Guidelines for Compounding Preparations.⁵ It does not represent the entire USP Chapter or the entire OCP Guidelines. For further information, please consult the complete version of USP Chapter <795> and the OCP Guidelines for Compounding Preparations respectively.

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