Ontario College of Pharmacists

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DRUG PREPARATION PREMISES FRAMEWORK

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Drug Preparation Premises Framework

Background

On May 15, 2013 the Ontario government announced a regulation authorizing the Ontario College of Pharmacists (the College, OCP) to inspect drug preparation premises (DPP) where pharmacists and pharmacy technicians engage in or supervise drug preparation activities. These **regulations** were initially drafted to address a gap in regulatory oversight that was identified as a result of the March 2013 allegations of under-dosing of chemotherapy drugs to Ontario and New Brunswick hospital patients. These regulations were drafted along with changes to the ***Public Hospitals Act*** which restricted where a hospital is able to purchase drugs[1]

A DPP is defined as any place where a member[2] engages in drug preparation activities, or where drug preparation activities take place that a member supervises, but does not include,

a) a pharmacy in respect of which a valid certificate of accreditation has been issued under the *Drug and Pharmacies Regulation Act*,

b) a premises in respect of which a valid establishment license has been issued under the *Food and Drugs Act* (Canada), or

c) a hospital or a health or custodial institution approved or licensed under any general or special Act[3].

Drug preparation activities are considered to be reconstituting, diluting or otherwise preparing a drug or combining, admixing or mixing together two or more substances, at least one of which is a drug, to create a final product for the purposes of the sale or provision to another person, other than pursuant to or in anticipation of a prescription.[4]

DPPs engage in drug preparation activities that can be described as non-sterile compounding and/or sterile compounding of non-hazardous and/or hazardous preparations. They provide preparations to a variety of facilities such as: hospitals, prescriber offices, ambulatory care clinics, veterinarians and community pharmacies.

The College does not accredit DPPs as it does community or hospital pharmacies. The regulations[5] allow the College to inspect DPPs, initially as part of a new DPP notification process. Registrants of the College are required to notify the College in writing if they will be engaging or supervising drug preparation activities at a DPP or in connection with the DPP. The completion of the **Notification to Engage in or Supervise Drug Preparation Activities** form will initiate the inspection process of a new potential DPP. A DPP that has two or more members engaged or supervising drug preparation activities at or in connection with a DPP, shall designate one member the designated member for the DPP and shall immediately notify the College of the designated member's identity[6]. The designated member will be the contact for all communications between OCP and the DPP.

The College inspects the DPP operations against the OCP **DPP Inspection Criteria**; the criteria are founded on the current legislation and established compounding standards of practice. The DPP Committee considers all matters relating to the operation of DPPs in Ontario. The DPP Committee, whose membership is the same as the Accreditation Committee of the College, review the findings of the DPP assessment and determines an outcome. Following an inspection there are three potential outcomes: pass, pass with conditions and fail. The College inspects DPPs annually after the initial assessment and more often if, in the opinion of the College it is necessary or as ordered by the DPP Committee. Only those facilities that have been assessed and have met the specified criteria are entitled to operate in the province. The results of a DPP inspection are posted on the public register on the College website.

The DPP framework provides three guiding principles that a DPP and registrants should adhere to, to ensure an environment and culture that promotes patient, compounding personnel and healthcare provider safety.

Three guiding principles of the DPP Framework:

1. Patient-centered outcomes
2. Safety-centred care
3. Professional accountability

Introduction

The compounding of medications has always been an integral part of the practice of pharmacy. While compounded preparations can provide an important treatment option(s) for patients, the act of compounding is not without risk. Compounding a drug is recognized as a Controlled Act in Ontario by the *Regulated Health Professions Act*[7].

Compounding can include preparing non-sterile preparations for topical use to complex sterile preparations for intravenous use or sterile ophthalmic preparations. Some examples of sterile preparations include the following types of medication: nasal inhalation solutions, respiratory therapy solutions, solutions for live organ and tissue or graft baths, injections (i.e. intramuscular, intravenous, intrathecal, intradermal, subcutaneous etc.), irrigation solutions for wounds and body cavities (i.e. thoracic, spinal, abdominal, pelvic), ophthalmic drops and ointments, otic drops for intratympanic administration, parenteral nutrition, dialysis solution, allergen extracts, topical preparations (where sterility is essential i.e. patients with burns) and radiopharmaceuticals.[8]

“The provision of high-quality compounded preparations does not just happen—it is the intentional outcome of structures and processes that are deliberately designed, organized, and executed. It is

founded on good science and a quality management framework, drawing on how people, supplies and equipment, processes, and the physical environment influence preparation quality."[9]

It is critical that DPPs have the necessary infrastructure (policies, procedures, facilities, equipment, and quality assurance programs) and compliance to ensure safe and quality compounded preparations. The quality and components in a final preparation cannot be verified through mere physical examination, for example viewing the final preparation. Compounded preparations may have quality issues such as: microbial contamination, excessive bacterial endotoxins, fungal contamination, and variability in the intended strength (sub-potent active ingredient or super-potent active ingredient), chemical & physical contaminants and ingredients of inappropriate quality. Pharmacy professionals can learn from unfortunate compounding errors that have occurred, been investigated, analyzed and follow the subsequent recommendations by investigators such as ISMP and/or professional bodies.

Registrants who decide to outsource preparations from a DPP must perform their own due diligence in selecting a DPP[10]. A distinction to note, the College inspects the operational processes of a DPP; the College does not approve the formulation or Beyond-Use-Date (BUD), inspect or test the preparations compounded by the DPP. The customer is responsible for ensuring that the vendor meets their explicit pharmaceutical requirements for the provision of their desired preparations. The registrants at the DPP will be held accountable for the compounded preparations that are provided to their customers.

Purpose

The purpose of this framework is to provide information and clarity regarding DPP services, legislative and practice requirements of a DPP. The three guiding principles inform DPPs and registrants of what is required to provide an environment and culture that promotes patient, compounding personnel and healthcare provider safety.

DPP Framework Guiding Principles

The three guiding principles are rooted in the **DPP Assessment Criteria** and professional accountabilities of registrants to promote safety for patients, personnel and healthcare providers.

1. **Patient-centered outcomes**
2. **Safety-centered care**
3. **Professional accountability**

1. Patient-centered outcomes

DPPs play an important role in enabling the patient's access to quality specialty compounded preparation. While DPPs do not have direct contact with the patient who receives the compounded preparations, they must be mindful that a patient ultimately receives their compounded preparation. The ultimate goal of the DPP preparations is to have the patient achieve the desired outcomes from their medications.

Example of a DPP sterile non-hazardous preparation: Potassium phosphate 15 mmol (phosphate) in 250 mL sodium chloride 0.9% for infusion to correct the patient's electrolytes with a positive outcome.

Example of a DPP sterile hazardous preparation: Cyclophosphamide 1 g in a 100 mL sodium chloride 0.9% minibag to be administered by to treat oncology patients with positive outcome.

To enable compounding personnel to provide the delivery of safe and effective patient-centered outcomes, a DPP must meet the inspection criteria, which includes:

- Compounding preparations according to evidence-based practices
- Having a quality risk management program
- Having a safe and effective workflow design
- Providing staff with the appropriate tools and resources
- Having thorough documentation processes
- Initiating practice improvements when deficiencies are identified
- Having a quality improvement process where errors are detected and corrected
- Being properly resourced with sufficient qualified staffing
- Having an emergency preparedness plan and business continuity plan to ensure continuity and minimize the potential for risk of interruptions in patient care due to unforeseen circumstances

2. Safety-centered care

Meeting the OCP DPP inspection criteria will ensure that the DPP has the required infrastructure, facilities, policies and procedures, quality assurance program and employee adherence to processes to ensure safe and quality preparations. The registrant will be held accountable for the integrity of the preparation, for example: concentration claims, stability and contamination-free. Inappropriate compounding practices can put employees and patients at risk for harmful outcomes.

To provide safety-centered compounding, the following are a few examples of what a DPP must have in place:

a) Compounding personnel must be able to consult a variety of up-to-date references to safely compound preparations. As a minimum, a DPP must have available the most recent editions of the following:

- *Standards, guidelines and policies of the College*
- *Trissel's "Handbook on injectable drugs"*
- *Relevant chapters of the United States Pharmacopeial Convention (USP) including Chapters 795, 797 and 800*

b) The inspection criteria state that the DPP should have written policies and procedures governing how a Beyond-Use Date (BUD) is determined for all compounded preparations. The National Association of Pharmacy Regulatory Authorities (NAPRA) states that the BUD, "must not exceed the earliest of the dates established by the following two criteria: expiration date based on chemical and physical stability according to reference texts and storage time related to risk of microbial contamination".[11] In summary, the BUD is based on chemical stability and microbial sterility. BUDs should be conservative and not based on word of mouth or extrapolation. The DPP will be held accountable to ensure that the BUD is evidence based.

Example: Where a stability study is done with a drug at a specific concentration (i.e. 1 mg/mL) in a specific vehicle (Vehicle A)

Extrapolation to another concentration (i.e. 20 mg/mL in Vehicle A) without any consideration of the outcome on the stability- should not occur ***OR***

Extrapolation to another vehicle (i.e. 1 mg/mL in Vehicle B) without any consideration of the outcome on the stability- should not occur

Evidence for determining the chemical stability should reference literature (i.e. package insert, references such as *Trissel's Clinical Pharmaceutics Database* or *King Guide to Parenteral Admixtures*, and stability studies published in peer reviewed journals) to obtain relevant stability, compatibility, and degradation information regarding the drug or its congeners. Literature and data indicating drug-specific and general stability should be consulted, consideration to the nature of the drug and its degradation mechanism, the container in which it is packaged, the expected storage conditions, and the intended duration of therapy must all be considered. BUDs should be reviewed periodically to ensure they are still appropriate due to new information (i.e. new published information, complaints or recalls).

BUD requirements are also based on the microbial risk level of the preparation being compounded. DPP personnel should determine the risk-level based on the risk of contamination due to complexity of the preparation, environment, types of ingredients and other processing procedures. Compounded sterile products prepared from non-sterile ingredients or components (i.e. beakers, vials) are always considered high risk. Professional judgment is required for other situations.

c) DPPs must perform a variety of risk assessments related to sterile and non-sterile drug preparation activities and document such activities. A risk assessment must be undertaken to identify the appropriate level of requirements to minimize contamination of each compounded product and to provide adequate protection for staff. The College will be requesting evidence of completed risk assessments for non-sterile and sterile preparations.

d) Sterility testing of preparations compounded using aseptic technique is an important quality check. The College will be reviewing evidence that a sterility test via membrane filtration and bacterial endotoxin test have been performed for:

i) High risk preparations in the following situation(s):

- When sterile preparations are compounded in batches over 25 identical units
- When there has been more than 12 hours of exposure time at a temperature between 2 and 8 °C before sterilization
- When there has been more than 6 hours of exposure time at a temperature above 8 °C before sterilization

ii) Compounded sterile preparations that have an extended BUD. The College will be seeking evidence that a validated sterility test has been performed and that there is acceptable stability data to support the extended BUD.

e) The College will review the documentation for a comprehensive quality assurance program, that minimally contains:

- Glove Fingertip Sampling (GFS) and media fill tests performed under real compounding conditions
- Sterile preparations that are compounded in compliance with procedures
- Verification of equipment, controlled areas, processes and final preparations
- Documentation of processes

f) Evidence of a robust environmental monitoring program will be reviewed by the College. The program should include: that room pressure(s) must be measured continuously (and include an alarm system to notify personnel of deviations) to ensure that differential pressures between controlled areas are kept constant, temperature readings of sterile compounding areas (ISO 7 and 8 areas) must be verified and documented at least once a day, and include a sampling plan (for controlled areas and PEC) for viable, non-viable and surface particles to be completed minimally every six months and monitoring humidity.

g) The College will inspect the labeling of final compounded preparation(s) to ensure they meet the following standards of practice:

- **NAPRA Model Standards for Pharmacy Compounding of Hazardous Sterile Preparations** and **NAPRA Model Standards for Pharmacy Compounding of Non-Hazardous Sterile Preparations** (Section 6.6.7)

- **NAPRA Model Standards for Pharmacy Compounding of Non-Sterile Preparations** (Section 6.7)

h) For increased safety, the DPP should give consideration to **ISMP TALLman lettering**, **ISMP Safety Bulletins**, **Good Label and Packaging Practices for Prescription Drugs** (a Health Canada and ISMP guide); all can be found at the **ISMP Canada** website.

i) The College will be inspecting the DPP to ensure that it meets having a secure, reliable and environmentally controlled (e.g. cold chain maintained) storage and transportation of the compounded preparations.

j) The College should not find evidence of the compounding of drugs that have been removed from the market due to safety reasons or preparations that are known to be difficult to compound. Consideration should be given to resources such as: Health Canada's website-**Recalls and Safety Alerts for Health Products** and **FDA 503 Bulk Substances List** .

3. Professional accountability

Pharmacists and pharmacy technicians as registrants of the College have professional accountabilities and responsibilities to uphold. Registrants may be employed at a DPP, supervising a DPP or involved in the purchase of preparations from a DPP. Registrants are required to adhere to the legislation, College policies and Code of Ethics and those who do not adhere may be subject to discipline by the College. Registrants of the College are responsible for the compounding of DPP preparations and further manipulations of such performed by registrants. For example: *Registrant at DPP compounds "Sterile Preparation "A" 10 mg/mL (100 mL) and Registrant at hospital, manipulates the DPP prepared Sterile Preparation "A", by further adding Drug "B" to the preparation.*

3.1. Registrants have a professional accountability to ensure that they adhere to all federal and provincial legislation, College policies, guidance and the Code of Ethics.

The following are examples:

a) Federal Acts and Regulations, examples below:

- **Controlled Drugs and Substances Act**
- **Food and Drugs Act**
- **Food and Drugs Regulations**
- **Personal Information Protection Electronic Document Act (PIPEDA)**
- **Privacy Act**

b) Provincial Acts and Regulations, examples below:

- **Drug and Pharmacies Regulation Act (DPRA)**
- **Pharmacy Act, 1991**
- **Regulated Health Professions Act, 1991, S.O. c. 18**

c) Health Canada policies, example below:

- **Policy on Manufacturing and Compounding Drug Products in Canada, POL-0051**

d) College policies, guidelines and the **OCP Code of Ethics**, examples below:

- **Guideline: Documentation**
- **Guideline: Extending the Beyond-Use Dates for Sterile Preparations**

e) Standards of practice, best practices, examples below:

- **NAPRA Model Standards of Practice for Canadian Pharmacists**
- **NAPRA Model Standards of Practice for Canadian Pharmacy Technicians**
- **NAPRA Model Standards for Pharmacy Compounding of Hazardous Sterile Preparations**
- **NAPRA Model Standards for Pharmacy Compounding of Non-Hazardous Sterile Preparations**
- **NAPRA Model Standards for Pharmacy Compounding of Non-Sterile Preparations**

f) Guidance documents, example below:

- **NAPRA Guidance Document for Pharmacy Compounding of Non-sterile Preparations**

g) Registrants should consider these supplemental resources:

- Canadian Society of Hospital Pharmacists (CSHP) website: **www.cshp.ca**
- CSHP official publication, for purchase **CSHP: Compounding Guidelines for Pharmacies (2014)**
- USP® website: **www.usp.org**
  - **USP Chapter 795 Pharmaceutical Compounding Non-Sterile Preparations**
  - **USP Chapter 797 Pharmaceutical Compounding Sterile Preparations**
  - **USP Chapter 800 Pharmaceutical Compounding Hazardous Drugs**
- U.S. Food and Drug Administration (FDA) website: **www.fda.gov** (i.e. Human Drug Compounding, Information for Outsourcing Facilities)
  - **FDA Compounding Laws & Policies**
- **National Institute for Occupational Safety and Health (NIOSH), NIOSH List of Antineoplastic and other Hazardous Drugs in Health Care Settings (2016)**

3.2 Responsibilities of Registrants employed at a DPP include:

a) The registrant who will be engaging or supervising drug preparation activities at or in connection with a DPP must notify the College by filing a **Notification to Engage in or Supervise Drug Preparation Activities.**

b) A registrant must notify the College in the event that the Registrant becomes aware that a Change of Control has occurred in respect of such DPP according to **College By-Law Article 18.1**

3.3 Responsibilities of healthcare professional (i.e. Registrant) purchasing preparations from a DPP:

a) The registrant and/or customer responsible for purchasing from a DPP should perform their due diligence in selecting a DPP It is recommended to form a working group or committee with expertise in materials management, risk management and pharmaceutical compounding to make this decision. Senior management and legal should also be part of this group or committee.

b) The OCP inspection report provides a snapshot captured during the DPP inspection visit. For a fulsome review, the registrant and/or customer should give consideration to include the following (at minimum) in their review:

- review DPP facility on the College website
- review College's inspection report(s) of the DPP (i.e. ask the DPP to provide)
- review if outstanding conditions have been remedied
- if purchasing narcotics, controlled drugs, benzodiazepines and other targeted substances from a DPP; ensure DPP has a Controlled Drugs and Substances Dealer's licence
- ensure evidence-based processes are utilized
- evidence based beyond-use dates
- review stability studies/in-house testing/sterility studies
- ensure required policies & procedures are in place (i.e. delegation for unregulated personnel)
- review and understand: sterility reports and in-house testing reports
- perform site visit during selection process

Recognizing that each DPP will have confidentiality requirements to view some reports.

c) Review resources to guide decision-making in selection of a DPP, for example:

- **Guidelines for Outsourcing Pharmaceutical Compounding Services: A Tool for Healthcare Organizations (2014)**

- **ASHP Guidelines on Outsourcing Sterile Compounding Services (2015)**
- Accreditation Canada, for purchase: **Accreditation Canada-Medication Management Standards**
- **ISMP Guidelines for the Safe Preparation of Compounded Sterile Preparations (2016)**
- **A Review of the Oncology Under-Dosing Incident**, Dr. J. Thiessen (2013)
- CSHP, member benefit: **Outsourcing: Guidelines for Pharmacy Practice (2011)**

d) Communicate with the DPP to ensure they are able to meet the explicit pharmaceutical service requirements of the customer.

e) Communicate with the DPP as to the intended purpose of the compounded preparation

- Both parties (the customer and DPP) need to understand how the customer intends to use the final compounded preparation
- The intended use by the customer, is a variable in the consideration of the BUD assigned by the DPP

f) Communicate with the DPP to understand how they are preparing the compounded preparation

- Is the DPP using Active Pharmaceutical Ingredient (API) instead of commercially available sterile products for a final sterile preparation? These would be high risk preparations made from non-sterile ingredients.

[1] Public Hospitals Act RSO 1990, RRO Reg 965 Hospital Management, 10.1
[2] member refers to a registrant of the Ontario College of Pharmacists, for example: pharmacist or pharmacy technician
[3] Pharmacy Act, 1991, Ontario Regulation 202/94, Part IX, S 53 (1) (b)
[4] Pharmacy Act, 1991, Ontario Regulation 202/94, Part IX, S 53 (1) (b)
[5] Pharmacy Act, 1991, Ontario Regulation 202/94, Part IX, S 54
[6] Pharmacy Act, 1991, Ontario Regulation 202/94, Part IX, S 58
[7] Health Professions Act 1991, 27 (2), 8
[8] NAPRA Model Standards for Pharmacy Compounding of Non-hazardous Sterile Preparations (2016)
[9] CSHP website, https://www.cshp.ca/compounding
[10] "A Review of the Oncology Under-Dosing Incident", Dr. Jake Thiessen (2013)
[11] NAPRA Model Standards for Pharmacy Compounding of Non-Hazardous Sterile Preparations 6.1.1