Addendum: Compounding methadone

Background

In Alberta, methadone should only be compounded in exceptional circumstances. Commercially manufactured methadone is available in the following formulations:

1. Methadose™ is available for use for opioid dependence.
2. Metadol™ is available for analgesia.

Health Canada provides the following guidance regarding compounding:

- Methadone should only be compounded if there is a specific **therapeutic need** or a **shortage of a commercially available product**, and should not be done solely for economic reasons that benefit the involved healthcare professionals.

- The compounded product must provide a customized therapeutic solution to improve patient care without duplicating an approved drug product.

For more information, please see Health Canada's Policy on Manufacturing and Compounding Drug Products in Canada at http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/pol_0051-eng.php.

Practice standards and responsibilities

Standards

Pharmacists and pharmacy technicians who compound methadone must comply with the following standards and responsibilities:

- Compliance with Health Canada's policy on manufacturing and compounding drug products in Canada.
- Be aware of changes to the laws that govern their practice and adjust their practices to ensure compliance with the changes. (S1.2, S1.3)
- Pharmacists and pharmacy technicians dispensing a Schedule 1 drug must ensure that they fill the prescription correctly, that they use appropriate dispensing procedures, that they properly package and label the drug, and that they perform a final check. (S7)
- Pharmacists and pharmacy technicians must compound according to a written compounding formula and a written preparation process. (S10)
- Pharmacists and pharmacy technicians must assign compounded products a beyond-use date and ensure that the products are not to be used after this date. (S10)
- A pharmacist or pharmacy technician who repackages drugs must take appropriate steps to protect patient safety. (S21)
- Pharmacists and pharmacy technicians must create and maintain appropriate patient records for dispensing and administration. (S18)
- Records must demonstrate an audit trail of staff involved in each process in the preparation, dispensing, and administration of the final product. (S7, S10, S21)
- Pharmacists must ensure that those whom they supervise act within the limits of their profession or training. (S20)

Responsibilities

- Pharmacists and pharmacy technicians must use proper equipment for compounding. Measuring devices must meet error allowances for weights and measures during the preparation of stock solutions and carries.
- For health reasons and risk mitigation, pharmacists and pharmacy technicians must not reuse carry bottles.
- In light of the potential of toxicity and lethality from errors involving methadone, pharmacies should organize their compounding areas and processes to optimize safety to staff and patients.
- The beyond-use date assigned to products must recognize the ingredients and the compounding processes. Pharmacies choosing to use beyond-use dates in excess of 14 days should provide support for stability and sterility from guidelines, published literature, or laboratory batch testing.
- A second qualified staff member should double check all preparations.
- Pharmacy staff should label and store all equipment used for compounding methadone separately from other equipment.
- Pharmacy staff should clearly identify methadone stock solutions, preferably using bottles, colours, or stickers that distinguish the preparation.
- There must be a working refrigerator on the premises to store prepared carries or other compounded methadone products. Pharmacy staff must monitor and routinely record the refrigerator temperature to maintain the cold chain.
- Pharmacists and pharmacy technicians involved in compounding methadone must remain responsible for the delivery of all components of activities that fall under the standards and expectations of their regulated profession.

Formulating methadone stock solutions

Pharmacists and pharmacy technicians are both authorized to compound and prepare methadone. Staff compounding methadone must be competent in the processes and use of equipment to compound the stock solution.

- Prepare methadone stock solution within a clean and organized environment following work processes that minimize the risk of error and mix-ups with other pharmaceuticals.

- Ensure that equipment or devices used to prepare the stock solution meet compounding standards for accuracy of measuring devices (e.g., glass graduated cylinders and oral syringes with marked volumes).

- If possible, pharmacies should label measuring equipment used to prepare methadone compounds and keep this equipment separate for the sole purpose of compounding methadone. If this is not possible, all equipment used must be properly washed and cleaned before reuse to prevent cross-contamination with other preparations.

- If possible, pharmacies should prepare only one standard concentration of methadone stock solution

most common to their patient population to minimize the risk of error. Common strengths include 1 mg/ml, 5 mg/ml, and 10 mg/ml.

- Label the stock solution distinctly. The label should include:
  - The ingredients and concentration of the solution (e.g., methadone 10 mg/ml stock solution in distilled water), and
  - The expiry date or use-by date of the solution.

  Note: If it is difficult to label the bottle distinctly, pharmacies can also use a distinct bottle.

- To avoid mix-ups, store compounded solutions in a separate area away from other solutions. Label and identify the compounded solution in such a way that it is visibly distinct from other solutions. This may include a distinct bottle with appropriate labeling. A boldly marked label and a poison sticker should be included in the labeling of the methadone solution.

The pharmacy must keep a bulk compounding log and record the following information for each prepared solution:

- Date prepared;
- Assigned batch number;
- Names (printed legibly) and signatures of personnel involved in preparing and/or checking the preparation;
- Name, quantity, lot numbers, and expiry dates of ingredients used to prepare the stock solution (e.g., methadone, distilled or bacteriostatic water, preservatives etc.);
- Concentration of the final solution;
- Volume of the final solution; and
- Expiry date or beyond-use date.

Stability of methadone

Methadone in powder form is very stable. Methadone has a long stability when distilled water is used as the diluent in preparing the stock solution. However, without a preservative, the shelf-life of methadone prepared in distilled water may be shortened; monitor for bacterial growth.

In spite of the excellent stability of methadone in distilled water, there can be variability in the compounding environment, processes, and techniques that can deviate from the conditions within a testing environment where published stability and sterility studies have originated.

Many factors can impact the sterility of the final product. Pharmacists and pharmacy technicians should base the stability and sterility of stock solutions on current evidence and consideration of pharmaceutical principles of compounding.

Attention has shifted to acknowledging the possibility of growth of bacteria or other pathogenic organisms within the prepared formulation. Therefore, the current recommendation is to discard stock solution prepared without a preservative after 14 days. This includes solutions prepared with distilled water.

For pharmacies choosing to prepare formulations with a preservative, methylparaben 0.5g/L or propylparaben 0.2 g/L are both appropriate preservatives with which to prepare stock solution.

Note: Published guidance on the stability of methadone solutions is reported in many provincial guidelines based on a study from the early 1990s. However, there is a need for more updated testing to acknowledge both the stability and sterility of prepared products under various compounding conditions.

Dispensing compounded methadone

Unless otherwise indicated by the prescriber, pharmacists must dispense all compounded methadone in a diluted juice or crystalline drink deemed compatible with the methadone. If the prescriber directs the pharmacist to deviate from this standard, the prescriber must provide and document a clear rationale on the prescription.

- Dilute the prescribed dose in approximately 100 ml of a coloured, flavoured vehicle such as Tang™ crystalline drink or Kool-Aid™. Plain water is not acceptable. Dilution in a 100 ml volume of flavoured drink will:
  - Mask the bitter taste of methadone,
  - Prevent abuse by injection due to the sugar content and exipients in the crystalline drink or juice, and
  - Discourage diversion.

- Dispensing guidelines within many provincial jurisdictions have identified the duration of stability of methadone in various diluents from a collection of past literature; however, the available literature has not addressed the issue of sterility which includes the likelihood of bacterial growth of the prepared solution stored under refrigerated or unrefrigerated conditions.

- To avoid the potential for mix-ups during dosing, formulations further diluted for administration should not be prepared far in advance. Additionally, given the variability in the compounding environment and processes, consider the aspect of bacterial growth within the prepared formulation.

Diluents

1. Methadone formulations that are prepared in advance for carries or witnessed dosing may use the examples of diluents listed in the table below. If stored under refrigeration, the preparation should be used within 14 days of compounding. If the product is prepared in

Allen's Apple Juice, discard it after seven days if stored under refrigeration.[1]

2. Formulations prepared in juices should have an expiry that does not exceed the shelf-life of the juice under the conditions of storage recommended upon opening the bottle. In general, dispensing methadone in fruit juices or diluents not identified below or within a product monograph is discouraged due to the lack of sufficient evidence for stability and sterility upon extended storage of the mixture, especially beyond immediate ingestion upon dilution.

3. Pharmacies may consider stability and sterility tests of their prepared formulations to support decisions to extend expiry dates beyond the guidance provided in this document. Pharmacies are encouraged to use reputable sources and to maintain records of their findings.

For more information on how to dispense medication-assisted treatment for opioid dependence, refer to ACP's ODT Guidelines.

Table 1: Methadone stability in various diluents for carries

Diluent	Stability at room temperature (20° to 25° C)	Period of stability at refrigerated temperature (5° C)	Period of acceptable sterility for oral consumption under refrigeration (i.e., bacterial or pathogenic growth)
Grape flavoured Kool-Aid™	17 days	55 days	• Unknown for compounded stock solution • 14 days for diluted Metadol™ preparations
Orange flavoured Tang™	11 days	49 days	• Unknown for compounded stock solution • 14 days for diluted Metadol™ preparations
Allen's Apple Juice™	9 days	47 days	• Unknown for compounded stock solution • 7 days for diluted Metadol™ preparations
Grape flavoured Crystal Light™	8 days	34 days	• Unknown for compounded stock solution • 14 days for diluted Metadol™ preparation
Grape flavoured Crystal Light™ with 0.1% sodium benzoate	29 days	Not available	• Unknown

Reference: Lauriault, G., M. J. Lebelle, B. A. Lodge, et al. "Stability of Methadone in Four Vehicles for Oral Administration." *Am. J. Hosp. Pharm* 1991 (48): 1252-1256.

1 Metadol™ product monograph (March 2009).

Bulk compounding record

Name and concentration: _____

Storage instructions & expiry: _____

Special instructions: _____

_____

Staff name (please print)	Initials (for file)	Staff name (please print)	Initials (for file)	Special instructions

Date prepared Batch #	Quantity used	Ingredient name	Lot #	Expiry date	Final strength	Final volume	Beyond-use date	Prepared by Checked by	Notes