# A Review of the Oncology Under-Dosing Incident

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**A Report to the Ontario Minister of Health and Long-Term Care**

**July 12, 2013**

# Executive Summary

The April 15, 2013 appointment by the Ontario Minister of Health and Long-Term Care (MOHLTC) as an independent investigator included the following mandate:

- To conduct a review to determine the causes of recently discovered instances of under-dosing of chemotherapy drugs (i.e., "incident") at Windsor Regional Hospital, London Health Sciences Centre, Lakeridge Health and Peterborough Regional Centre;
- To provide recommendations to prevent future incidents of this nature;
- To provide a report to the Minister of Health and Long-Term Care no later than July 12, 2013.

The investigation was launched at the above affected Ontario health care institutions, along with clinical sites associated with the New Brunswick Department of Health and its Horizon Health Network. The review also examined the engagement by various stakeholders in the incident. This included the two primary linked organizations associated with the oncology medication incident (i.e., the Group Purchasing Organization [Medbuy] and the vendor [Marchese Hospital Solutions]). Furthermore, the evaluation included various additional key professional, structural, regulatory and oversight stakeholders (i.e., the Ontario Ministry of Health and Long-Term Care, Health Canada, Cancer Care Ontario, the Ontario College of Pharmacists, and the Ontario Hospital Association).

The investigation sought to determine the root cause for the under-dosing, to evaluate how hospitals responded to the incident, to study the broader realm of pharmaceutical product preparation, and to examine the systemic influence of professional, structural, regulatory and oversight stakeholders.

The major findings were as follows:

1) The under-dosing incident was initially discovered on March 20, 2013, and the incident specifically involved the use of the oncology medications known as CYCLOPHOSPHAMIDE and GEMCITABINE.
2) In total, 1202 patients were affected. Of these, 1007 were under-dosed with CYCLOPHOSPHAMIDE, 191 were under-dosed with GEMCITABINE, and 4 received both oncology medications. The largest fraction (1162) were adults, and the remainder (40) were pediatric cases. All but 30 patients were being treated for cancer.
3) There is no evidence of any malicious or deliberate drug-sparing dilution by Marchese Hospital Solutions (MHS) in preparing their bags of CYCLOPHOSPHAMIDE or GEMCITABINE. MHS employed a process in the preparation of the bulk reconstituted CYCLOPHOSPHAMIDE and GEMCITABINE that failed to compensate adequately for an overfill factor in the supplier's normal saline bags. On the basis of the MHS labels on the bags (4000 mg per 100 mL bag for GEMCITABINE; 4000 mg per 200 mL bag for CYCLOPHOSPHAMIDE), the best estimate is that the average actual CYCLOPHOSPHAMIDE concentration was 10% lower than that stated on the label. For GEMCITABINE the average actual concentration was 7% lower than stated on the label. In the absence of clarifying patient-related instructions by MHS to the hospitals, the hospitals were not aware of the need to adjust doses accordingly to factor in the aforementioned lower concentrations. Thus, the overfill issue led directly to the patients under-dosing for both GEMCITABINE and CYCLOPHOSPHAMIDE.

4) After the discovery of the lower dosing, the hospitals faced a major challenge in addressing this issue. The present infrastructure and personnel within each hospital met and largely overcame this challenge. Evidence supports the view that the hospitals performed well in this crisis. The questionable medications were immediately removed from further patient use, and back-up plans brought the pharmacy-based medication preparation in-house, such that no patient missed a scheduled dose. Overall, the responses by administrators, physicians, pharmacists, nurses, and other personnel were timely, innovative, and demonstrated primary concern for the patients. These professionals are a credit to our health care system.
5) The decisive steps taken, whether in hospitals or through provincial or national stakeholder agencies, demonstrated commendable crisis-stemming leadership. There was a concerted resolve to address the issues squarely and urgently, and to avoid further complicating incidents that might threaten patients' care.

As a result of the findings that encompass this oncology incident, other related spheres of medication management, and the system of identifiable stakeholders, the following recommendations are presented (further details are found within the report):

## Recommendation #1:

Notwithstanding the under-dosing incident, the continued use of Group Purchasing Organizations (GPOs) to negotiate vendor product preparation pharmaceutical services shall not be discouraged. However, improvements are needed in the GPO-based processes.

## Recommendation #2:

Every GPO shall review its procurement process to ensure that risk for patients is considered an essential evaluation and adjudication criterion when considering proposals.

## Recommendation #3:

Every GPO shall develop and adopt a standardized product and/or service specification description that outlines the requirements for contracted sterile or non-sterile pharmaceutical preparation services.

## Recommendation #4:

Annually in January, each GPO shall publicize information regarding the contracted pharmaceutical services provided by all its vendors.

## Recommendation #5:

Marchese Hospital Solutions (MHS) shall review and revise its product preparation processes to ensure that all its products meet the specifications required by professionals in treating patients effectively and safely.

## Recommendation #6:

The Ontario College of Pharmacists (OCP) (and by extension, the National Association of Pharmacy Regulatory Authorities [NAPRA]) shall work quickly with Health Canada to define best practices and contemporary objective standards for non-sterile and sterile product preparation within a licensed pharmacy.

## Recommendation #7:

The OCP (and by extension, NAPRA) shall stipulate specialized electronic material records and label requirements for non-sterile and sterile product preparation within a licensed pharmacy.

## Recommendation #8:

The OCP (and by extension, NAPRA) shall consider a special designation and licence for any licensed pharmacy engaged in large volume non-sterile and sterile product preparation. Such pharmacies shall be inspected annually.

## Recommendation #9:

The OCP shall specify credentials beyond education and licensing for personnel engaged in non-sterile and sterile product preparation practices within a licensed pharmacy.

## Recommendation #10:

Health Canada shall license all enterprises that function beyond the product preparation permitted within a licensed pharmacy; that is, all product preparation enterprises not within a licensed pharmacy shall be licensed.

## Recommendation #11:

The Ontario Hospital Association (OHA) shall conduct a formal review/audit to determine the efficiency and traceability of computer-based clinic and hospital records for patients and their treatments, and report the findings to the MOHLTC.

## Recommendation #12:

The OCP shall license all pharmacies operating within Ontario's clinics or hospitals.

This review has uncovered the cause of the oncology under-dosing. The recommendations are intended to prevent future oncology incidents of this nature and to mitigate identifiable risks in the broader realm of non-sterile and sterile product preparation within licensed pharmacies and other enterprises.

# Table of Contents

# 1. Introduction

To be diagnosed with cancer is devastating for most people. It causes uncertainty, fear of the unknown, and a certain loss of control over their own destiny. Their desire for trusted, reliable advice and intervention from medical personnel becomes paramount.

Chemotherapy is generally accepted to be one strategy in combating the disease. The underlying principle of the approach is to kill the cancer by treating it with chemicals that interfere with vulnerable processes surrounding cell division. Medicines do this either by damaging important proteins involved, or by damaging the DNA itself (DeVita and Chu 2008; Yap, Amlin and de Bono 2013). While chemotherapy drugs are effective against cancer cells because these cells divide rapidly, they unfortunately affect normal cells that also undergo rapid division. These include cells associated with the bone marrow, immune system, gastro-intestinal tract and hair follicles. As a result, chemotherapy frequently brings unwanted side effects such as nausea, hair loss, pain and vomiting.

Diverse classes of chemotherapy drugs work by interfering with different stages of cell division. To take advantage of this, doctors often prescribe them as “combination therapy”, so that the treatment is more effective. Most standardized chemotherapy treatment programs aim to be aggressive in attacking the cancer cells, but try to spare the individual’s normal body functions. Delicately balancing the beneficial and adverse effects illustrates the art of medicine versus the theoretical science. Furthermore, cancer treatment is increasingly personalized (Gonzalez de Castro, et al. 2013; Tian, Price and Hood 2012). That is, treatment is adjusted to accommodate each person’s unique clinical, genetic, genomic, physiologic, biologic and environmental information (Vesell 1982; Benet, Kroetz and Sheiner 2005), as well as the nature of the cancer (Gasparini and Longo 2012). The size and age of the patient is also important in the treatment plan (Kumar Pal and Hurria 2010). The size metric for such decisions is not universally agreed upon (Gurney 2002; Field, et al. 2008), but body surface area (BSA) is a common basis for tailoring the size of the dose. Identifying BSA is associated with some error (Field, et al. 2008), which means that doses cannot be precisely based on this metric. Uncertainty or “margin of error” is therefore inherent in chemotherapy, even during the early stage of intervention therapy.

Notwithstanding the above science or art, there is the very real issue of patient anxiety about cancer therapy. Where does the individual turn for assurance? Commonly, an implicit trust is placed in the doctor or medical team. Emotional stability is greatly influenced by the conviction that the individual is receiving the best treatment plan; that is, given all the variables, the plan is carefully tailored for optimal results. News that a dilution of chemotherapy has led to under-dosing is understandably upsetting and clearly a violation of the expectation for an optimized plan and the aforementioned trust. The emotional trauma experienced by the patient and caregiver(s) can be overwhelming.

# 2. Background/Context

*"Our lives begin to end the day we become silent about things that matter."*

**Martin Luther King**

The request to serve the Ministry of Health and Long-Term Care as an independent reviewer[1] of a chemotherapy dilution incident ultimately led to an official appointment on April 15, 2013. The appointment specified the following:

- Conduct a review to determine the causes of recently discovered instances of under-dosing of chemotherapy drugs at Windsor Regional Hospital, London Health Sciences Centre, Lakeridge Health and Peterborough Regional Centre;
- Provide recommendations to prevent future incidents of this nature;
- Provide a report to the Minister of Health and Long-Term Care no later than July 12, 2013.

At the date of the appointment, this reviewer was informed about the under-dosing only to the level of the average citizen; specifics surrounding the entire matter were unclear. Nonetheless, the implication of media reports was that a serious incident had occurred and that patients were the victims.

An early analysis of the issues underscored the need to gain first-hand, evidence-based information that should be validated wherever possible. It was important to approach the review without a preconceived bias regarding stakeholder guilt or innocence.

The review approach was to pursue the available evidence via a hybrid of the Kipling Method of Inquiry and Root Cause Analysis.

Rudyard Kipling (Nobel Prize for Literature in 1907) wrote:

*I keep six honest serving men*
*(They taught me all I knew);*
*Their names are What and Why and When*
*And How and Where and Who.*

Root Cause Analysis (RCA) is designed to answer three basic questions following a critical incident or adverse event in health care: what happened, why it happened, and what can be done to reduce the likelihood of it recurring[2]. However, RCA does not directly address a fourth question; namely, has the risk of future event recurrence actually been reduced? This last question customarily requires an extended period of time to determine whether there is a recurrence of an incident.

[1] An abbreviated biographical sketch can be found in Appendix 1.
[2] Via Canadian Patient Safety Institute: Jennifer L. White. Root Cause Analysis: A Review of the Relevant Literature.

# 3. Objective

## a. The Focus for the Initial Stage of the Investigation

In view of the serious implications of the discovery for patients, the quest began fundamentally at the level of patient care. The objective was simply to gather information about the incident (see Figure 1) and to substantiate evidence and outcomes. In keeping with the approach, the objective was to learn precisely what happened, when it happened, why it happened and who was responsible. It was also considered important to learn how the episode had been dealt with, as this incident was not only about materials; that is, chemotherapy agents, but more importantly about affected patients.

To begin with, each of the involved Ontario hospitals was visited beginning at "ground zero" where the discovery was made (i.e., Peterborough Regional Health Centre); the New Brunswick institutions were also contacted. Thereafter, the search was expanded to other stakeholders, like the vendor (Marchese Hospital Solutions [MHS]), the Group Purchasing Organization (Medbuy), followed by those that would be considered to have professional or regulatory oversight (see Figures 1 and 2). The schedule of visits and conference calls is shown in Appendix 2.

At the level of the hospitals, each visit included a spectrum of personnel that had a direct association with the incident. In an arranged meeting onsite, the individuals present typically included the President/CEO, administrative leaders, oncology medical personnel, nurses, pharmacists and their assistants, and risk management personnel. The formalized interview involved a detailed examination of the event using a battery of questions. The following topics illustrate the evidence pursued:

- Hospital organizational structure; reporting; accountabilities
- Pre-determined emergency plan (as applied to the incident); personnel involved
- Outsourcing suppliers including Medbuy; reason(s) for outsourcing, responsibilities, controls
- Connections with the GPO and vendors (past and present)
- Discovery of the incident; evidence; observations; decision-making; personnel involved; contacts; reporting; contingency plan; safeguards for patients
- Finding and contacting affected patients; revised treatments; exercising the emergency plan; changes implemented as a consequence
- Dealing with trust both with patients and within hospital staff; media contacts

Following the interview meeting, the pharmacy site associated with the preparation of oncology medications was inspected to learn particularly how their medications were prepared or processed, the operational features, and quality controls. The relationship between products and their clinical use was also reviewed. This included a visit to the clinic where patients received their medications. The intent was to learn about the controls to ensure a patient received the specified medication at the right dose and time.

Figure 1 shown below represents the initial focus of the investigation.

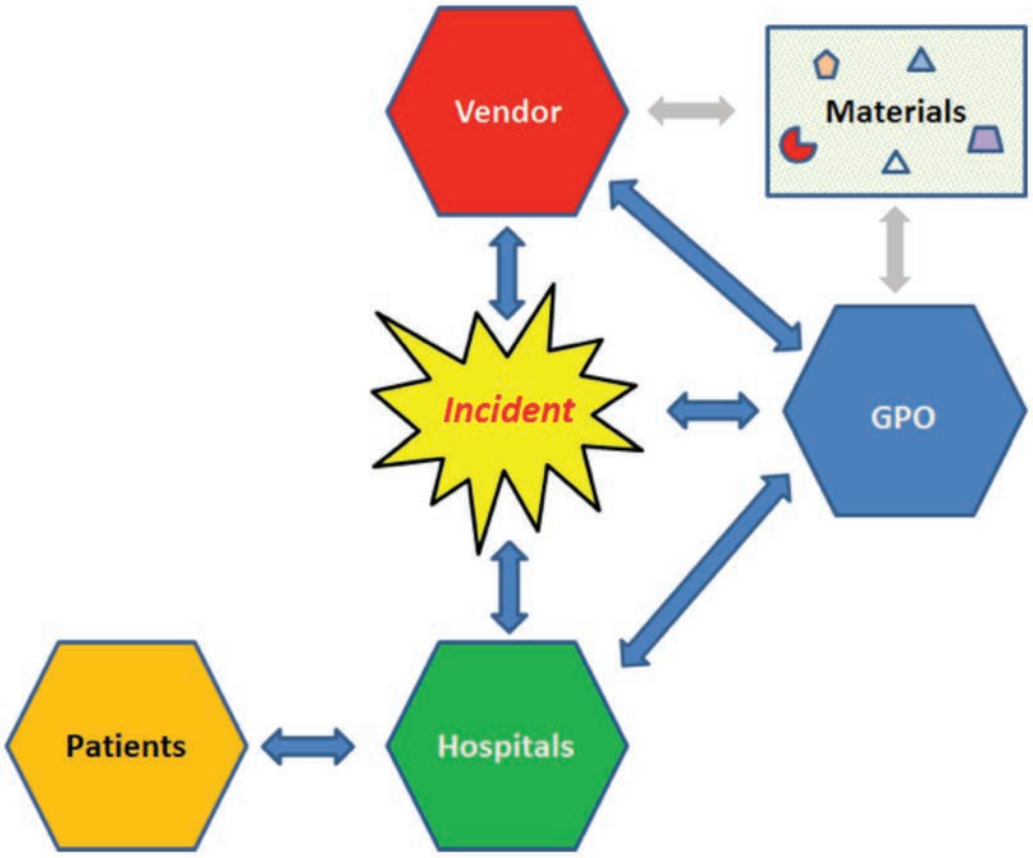


Figure 1: View of the primary, directly linked stakeholders associated with the oncology medication incident.
[GPO = Group Purchasing Organization (Medbuy)]
[Vendor = Marchese Hospital Solutions (MHS)]

Figure 2 below presents the enlarged group of stakeholder organizations.

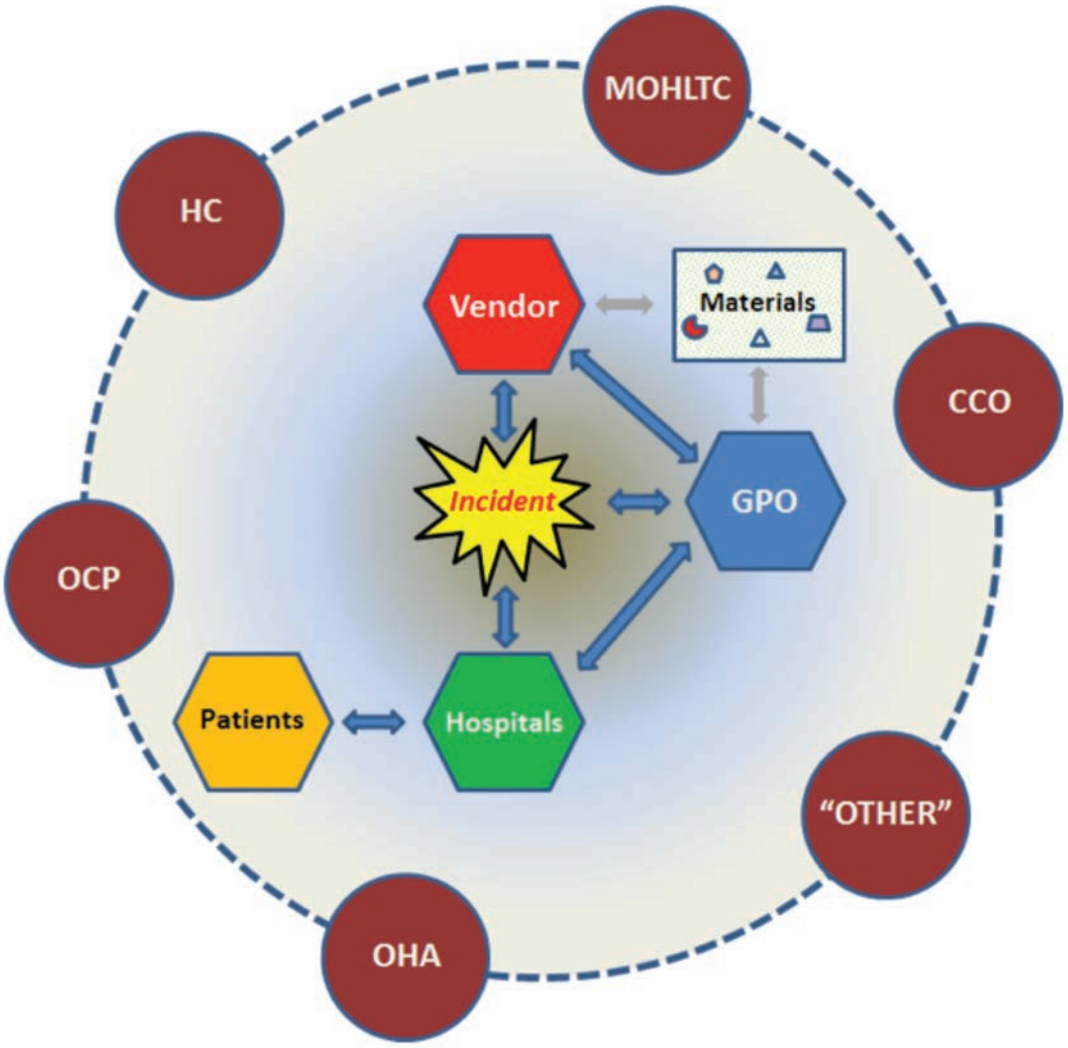


Figure 2: View of additional key professional, structural, regulatory, and oversight stakeholders associated with the oncology medication incident.
[GPO = Group Purchasing Organization (Medbuy)]
[Vendor = Marchese Hospital Solutions (MHS)]
[MOHLTC = (Ontario) Ministry of Health and Long-Term Care]
[HC = Health Canada]
[CCO = Cancer Care Ontario]
[OCP = Ontario College of Pharmacists]
[OHA = Ontario Hospital Association]

# 4. Observations from the Investigation

*"Trust makes life work. We eat food prepared by others, drive on roads built by others; we rely, every day, on actions of others, and we are relied upon in turn. Where trust fails chaos closes in. Our entire civilization relies on a singular faith that we can count on others…."*

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## a. Response to the Incident

### *i. Response at the hospitals*

The early days of the incident began with the discovery of a questionable MHS GEMCITABINE product on March 20, 2013 at the Peterborough Regional Health Centre. This discovery was shared with Lakeridge Health on the same day. Lakeridge Health contacted London Health Sciences Centre (LHSC) on March 22, 2013. This institution contacted Windsor Regional Hospital on March 27, 2013. The same day, Marchese informed New Brunswick regarding questions in Ontario about their products. LHSC in turn notified CCO on March 27, 2013, and CCO contacted the MOHLTC on March 28, 2013.

The above information was gained following the launch of the visits and/or calls identified in Appendix 2. The reports from each institution provided clear evidence of systems that could deal with emergencies. The implementations yielded rapid and quality responses. Upon discovery of questionable oncology medications, pharmacy personnel exercised alerts to other institutions that were not part of any formal structure, but simply part of their inherent professional connections. The alerts quickly served to identify the locations receiving the MHS "bulk reconstituted" products. Thereafter, the pharmacy personnel, whether at ground zero (i.e., Peterborough) or in hospitals subsequently alerted, took every measure to remove the questionable products immediately from any further patient use. Each of the institutions quarantined these products. In carefully exploring this action, each institute was able to account for all products based upon their record of use and the quarantining. The hospitals agreed to retain these in quarantine until such a time that they might officially be disposed of. Each of the pharmacy teams promptly launched a back-up plan, creating their own complete in-house preparation of the products for administration. Functionally, this meant the reconstitution of the CYCLOPHOSPHAMIDE and GEMCITABINE from the pharmaceutical manufacturers' supplied drug vials. These products were processed in accordance with customary procedures. The CYCLOPHOSPHAMIDE and GEMCITABINE used in the hospitals were from the same GPO-directed supply that had been used by MHS. The outcome of this quick response was that no patient missed any of their scheduled CYCLOPHOSPHAMIDE and GEMCITABINE doses.

Next, in each hospital, a risk management plan was immediately implemented. The institutions searched their databases to find the affected patients as quickly as possible. This was not a straightforward exercise in some cases. The reason is that all medication entry, patient entry, and treatment records were not in one integrated computer system. Valiant efforts were observed in locating the identities of patients, with hospital personnel sometimes combing through three separate computer record systems. An integrated system would have made the search rather simple provided the medication entry information was comprehensive (this matter is addressed in the Recommendations section). Once patients had been identified, strategies for contacting them included phone calls, announcements, and registered letter mailings. Wherever possible, physicians telephoned the patients or arranged for them to come into the clinics or hospitals. Help lines were organized and call-ins were encouraged. Where beneficial, efforts were made to contact the media so that further alerts could be sent out. In some cases, town hall meetings were organized to provide added opportunities to share information and answer questions. The commitment and diligence by administration, risk management personnel and other hospital personnel was generally exemplary. It should be remembered that such actions were taken in the backdrop of the customary daily workload of patient care.

Not surprisingly, diverse emotions were observed among patients. Some were extremely grateful for the actions the hospitals had taken. However, some patients and caregivers showed anger and resentment. Questions about death riveted the concerns as some patients had already passed away. The frequent question was whether the dilution problem might have contributed to a perceived premature death. Some of these anxieties and concerns were particularly palpable when the cancer victim was a child.

On the basis of the verified counts at the affected hospitals, the identified patient numbers are summarized in Table 1.

Table 1: Patient Numbers at the Affected Hospital Locations

| Location | Number of Patients |
|---|---|
| Peterborough Regional Health Centre | 1 |
| Lakeridge Health | 37 |
| London Health Sciences Centre | 691 |
| Windsor Regional Hospital | 290 |
| New Brunswick | 183 |
| Total | 1202 |

Further information regarding the CYCLOPHOSPHAMIDE or GEMCITABINE used in these 1202 patients is presented in Appendix 3.

The general evidence is that the mobilized action plan by administration, clinicians, risk management personnel, and a variety of other hospital staff was exemplary. Uncommon diligence and commitment was displayed in connecting with patients (e.g., physicians, despite their normal busy practices; administration; nurses; risk management; town hall meetings; mailings; etc.).

Finally, each of the hospitals also became part of a broader immediate information alert to CCO and the MOHLTC.

**Summary Finding #1**

The present infrastructure and collection of personnel within each hospital met and largely overcame the challenge associated with the oncology medication incident. Evidence supports the view that the hospitals performed well in this crisis. The questionable medications were immediately removed from further patient use, and back-up plans brought the pharmacy-based medication preparation in-house, such that no patient missed a scheduled dose. Overall, the responses by administrators, physicians, pharmacists, nurses and other personnel were timely, innovative and demonstrated primary concern for the patients. These professionals are a credit to our health care system.

All data surrounding each hospital's involvement with the incident (Ontario and New Brunswick), from the date of discovery until June 30, 2013, has been reviewed; comparative chronological evidence served both to link and validate the individual hospital's claims and actions.

## *ii. Response by Oversight Organizations*

The response by the stakeholders (Figure 2) to the incident was assessed partly by learning of their views and actions through the Working Group meetings. Perhaps more enlightening were individual visits and calls that examined further elements of the organizations and their actions. Typically, as with the hospitals, this included a formalized interview involving a detailed evaluation of the event using a battery of questions.

An overview of evidence, beginning from the surfacing of the incident, shows that several important actions were completed to ensure a safe and risk-minimizing outsourced product network. The following summarizes some of the developments.

Upon discovery of the questionable oncology medications and the attending implications for the affected patients, the MOHLTC rapidly organized a Working Group composed of the key professional, structural, regulatory and oversight stakeholders associated with the oncology medication incident (Figure 2). An exemplary collaborative agency plan unfolded that included daily calls with updates to make certain that information was shared by all, including ongoing actions or developments. The Working Group's members individually took control and instituted jurisdictional steps to deal with the issues and attempt to mitigate further risk.

The MOHLTC, HC and the OCP took timely action about remedial clarifications encompassing the structural and operational requirements for outsourced suppliers/vendors. The following information highlights some of their actions:

- The MOHLTC sought to determine what outsourced suppliers were being used by hospitals; attestations were requested to ensure that only suppliers with predetermined qualifications would be servicing the hospitals.
- Subsequently, the MOHLTC amended Regulation 965 under the Public Hospitals Act (See Appendix 5). Briefly, among several defined constraints, this amendment restricted medication preparation to:
    - An accredited pharmacy under Ontario's Drug and Pharmacies Regulation Act
    - A person licensed under the federal Food and Drugs Act
    - An accredited pharmacy in another Canadian jurisdiction
    - A drug preparation premises that passes an inspection by the Ontario College of Pharmacists.
- The OCP also announced regulatory and bylaw changes; an amendment was announced to Ontario Regulation 202/94 (See Appendix 5). In this change, a new section was added (Part IX: Inspection of Drug Preparation Premises [DPPs]). Briefly, this amendment with an accompanying bylaw provided the College with the authority to inspect DPPs where pharmacists and pharmacy technicians work. The announcement outlined the parameters, including timelines, of how a member is to notify the College of current or intended employment in a DPP.
- Health Canada also provided official regulatory direction to organizations involved in any compounding and admixing of medications, specifying that one of the following three conditions must prevail:
    - Done within a hospital, meeting provincial regulatory requirements
    - Done, outside a hospital, as a service under the supervision of a provincially licensed pharmacist, or
    - Done in a manner that meets the licensing and manufacturing requirements of the federal Food and Drugs Act

The concern and intent to act quickly by all key professional, structural, regulatory, and oversight stakeholders associated with the oncology medication incident was clearly evident.

### Summary Finding #2

The decisive steps taken, whether in hospitals or through provincial or national agencies, demonstrated commendable crisis-stemming leadership. There was a concerted resolve to address the issues squarely and urgently, and to avoid further complicating incidents that might threaten patients' care.

All interview and chronological data gathered from the stakeholders, from the date of discovery until June 30, has been reviewed and linked so as to validate the claims made, progressive steps, and actions taken.

## b. Medications (Materials) Associated with the Incident

*Quality is never an accident; it is always the result of high intention, sincere effort, intelligent direction and skillful execution; it represents the wise choice of many alternatives.*

**William A. Foster**

This review of the medication issue is directed primarily at the CYCLOPHOSPHAMIDE and GEMCITABINE dose preparation that led to under-dosing. The incident (see Figure 1) may best be understood in a comparative way; that is, to evaluate what happened in the preparations of doses by the previous vendor (Baxter), the new vendor (Marchese Hospital Solutions), and now occurring in-house at the affected hospitals.

This synopsis will present first the materials and then the comparative methods of processing them. To begin with, the pharmaceutical manufacturer medication vials used by all three organizations are shown in Figure 3. The drug in each vial is in the form of a dry, lyophilized powder.

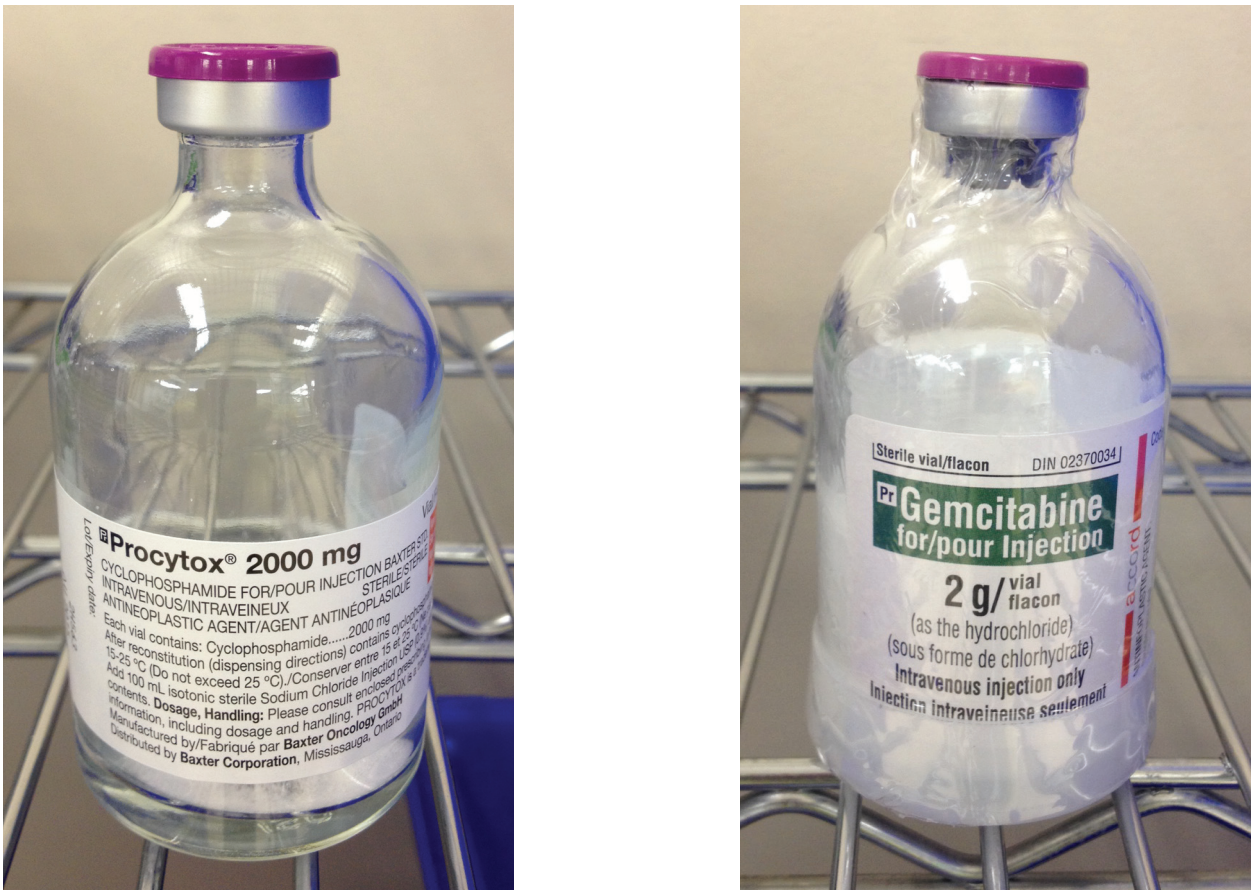


Figure 3: View of the 2000 mg (2 gram) CYCLOPHOSPHAMIDE (Baxter) vial [left], and the 2000 mg (2 gram) GEMCITABINE (Omega Laboratories) vial [right].

In making the comparison, the following provides background information regarding the materials.

## *i. Pharmaceutical products*

Both the vendors and the hospitals used the same source for intravenous CYCLOPHOSPHAMIDE (Baxter) and GEMCITABINE (Omega). These were Health Canada approved medications. This information shows that there was no distinction between the vendors and the hospitals in that only quality, contractually specified pharmaceutical materials were used by all for the preparation of the patient doses.

## *ii. Diluents used with the pharmaceutical products*

An important factor is the diluent used in dissolving (i.e., reconstituting) the powder in the manufacturers' vials to create the sterile, concentrated CYCLOPHOSPHAMIDE and GEMCITABINE solutions. Both the vendors and the hospitals used only Health Canada approved diluents, which in this case is sterile 0.9% sodium chloride (normal saline) for intravenous administration. The distributor source of the normal saline was either Baxter or Hospira. The diluent came in various bag sizes; the size used was defined by the reconstitution process. Both the vendors and the hospitals all used the drug product monograph specified technique for reconstituting the powder in the vials. Fundamentally, all employed the same technique and the same fluid volumes to dissolve the CYCLOPHOSPHAMIDE and GEMCITABINE. There was no difference in the preparation method and no difference in the reconstitution volume of normal saline used.

It is noteworthy that this stage of dissolving the drug powder in the vials may consume considerable time. This is an important reason why outsourcing through vendors is used by the hospitals. In a busy oncology service where many doses are prepared daily for patients, waiting for a drug to dissolve is a substantial inconvenience.

Table 2 on the next page compares the initial and subsequent steps for CYCLOPHOSPHAMIDE (C) and GEMCITABINE (G) dose preparation.

Table 2: A Comparison of the CYCLOPHOSPHAMIDE (C) and GEMCITABINE (G) Reconstitution Procedures

| Step | Hospitals | Baxter | Marchese |
|---|---|---|---|
| Step #1 | Assemble materials:<br>• Vials of C or G;<br>• Bulk normal saline solution | Assemble materials:<br>• Vials of C or G;<br>• Empty ViaFlex infusion bags;<br>• Bulk normal saline solution | Assemble materials:<br>• Vials of C or G;<br>• Pre-filled Hospira normal saline bags; 100 mL bags for G and 250 mL bags for C |
| Step #2 | Reconstitute the C or G vials using monograph specified volume of normal saline:<br>• Use 50 mL for each 2000 mg G vial;<br>• Use 100 mL for each 2000 mg C vial | Reconstitute the C or G vials using monograph specified volume of normal saline:<br>• Use 50 mL for each 2000 mg G vial;<br>• Use 100 mL for each 2000 mg C vial | Reconstitute the C or G vials using monograph specified volume of normal saline:<br>• For the G, use the contents from the 100 mL bag; use 50 mL for each 2000 mg G vial;*<br>• For the C, discard 50 mL from the 250 mL bags; use 100 mL for each 2000 mg C vial* |
| Step #3 | No Step #3 | Create bulked reconstituted C or G:<br>Add the reconstituted C or G to an empty ViaFlex infusion bag:<br>• For G, use 2x2000 mg in 100 mL bags (total volume actually 105.26 mL); weigh bags to provide a quality check on volume contents;<br>• For C, use 2x2000 mg in 200 mL bags (total volume 200 mL); weigh bags to provide a quality check on volume contents | Create bulked reconstituted C or G:<br>Add the reconstituted G and C back to the above normal saline bags:<br>• For G, use 2x2000 mg in 100 mL bags;*<br>• For C, use 2x2000 mg in 200 mL bags (total volume 200 mL)* |
| Step #4 (only in hospital) | Draw up the needed total dose from the prepared C or G vials and dilute into a normal saline bag for administration to the patient | Draw up the needed total dose from the Baxter bulk reconstituted C or G vials and dilute into a normal saline bag for administration to the patient | Draw up the needed total dose from the Marchese bulk reconstituted C or G vials and dilute into a normal saline bag for administration to the patient |

*This is where the difference exists. Marchese did not adjust adequately for the overfill volumes in both the 100 mL and 250 mL bags from Hospira.

The comparison in Table 2 shows that the primary difference exists in Step #3, which is to create a bulk reconstituted solution of the drugs; this step is avoided by the hospitals. In comparing the process used by Baxter and Marchese, Baxter used an empty bag to combine the bulk reconstitution of G or C, while Marchese used the prefilled normal saline bags. These prefilled normal saline bags had overfill, which led to an excess final fluid volume in the bags for both G and C. The Baxter process ultimately defined the concentration of G or C through the filling into the empty bags. However, in the Marchese process, it was assumed the G or C was present in 100 mL or 200 mL, respectively. This overlooked the residual volume remaining in the bags due to overfill. Practically, without knowing the final concentration in the Marchese bags, the overfill disguised the somewhat lower concentration in the normal saline. As a result, in drawing up the dose based on the label's claims at the hospitals (in Step #4), the Marchese bulk solutions provided a substandard dose.

### *iii. The Difference Factor*

The clear difference factor in bulk reconstitution preparation lies in the overfill within the normal saline bags used in hospitals and by MHS. That is, although a bag may be nominally labeled to contain 100, 250, 500 or 1000 mL of 0.9% sodium chloride, the actual volume may be somewhat larger. Such overfill is widely known and is not limited to diluents[3]. For example, Baxter had declared its overfill (shown in Appendix 4). Both the GPO and MHS were apparently aware of such overfills. The degree of overfill is not standardized; it becomes part of a manufacturer's finished product specifications. The reason for this overfill is that the fluid bags are to some extent permeable to water. That is, water can move through the membrane and then evaporate from the outside surface. On storage, the contents of the bags can thereby decrease. The product's shelf life is defined by the length of time it would normally take before the contents are reduced to the aforementioned nominal contents (e.g., 100 mL) on the label. Obviously, the rate of loss is determined by the permeability of the bag, fluid volume to surface ratio, and the storage conditions. This influences both the overfill variability used by a manufacturer and the contents determined at any point in time.

Hospira, which supplied the diluent (0.9% sodium chloride) to MHS, had provided their finished product testing results for overfill for the batches used in processing the MHS chemotherapy drugs. Table 3 shows the average overfill results, obtained from their United States analytical site. This information does not include the degree of variability. Nevertheless, it does permit a reasonable estimate of the anticipated average concentration of CYCLOPHOSPHAMIDE and GEMCITABINE in the bags prepared by MHS.

[3] Example: Pharmaceutical Law & Industry Report, Vol. 6, No. 30, 07/25/2008. Copyright © 2008 by The Bureau of National Affairs, Inc.

Table 3: Hospira Overfill for Its Saline Bags

| Nominal Volume (mL) | Batch | Average Tested Volume (mL) | Overfill (%) |
|---|---|---|---|
| 100 | 09025JT | 106.9 | 6.9 |
| 100 | 11154JT | 107.0 | 7.0 |
| 100 | 13036JT | 107.0 | 7.0 |
| 100 | 15157JT | 107.0 | 7.0 |
| 100 | 18038JT | 107.1 | 7.1 |
| 100 | 21052JT | 107.0 | 7.0 |
| 100 | 23128JT | 106.8 | 6.8 |
| 250 | 11136JT | 270.4 | 8.2 |
| 250 | 15087JT | 270.5 | 8.2 |
| 250 | 19084JT | 270.5 | 8.2 |
| 250 | 24012JT | 270.4 | 8.2 |
| 500 | 10722FW | 541 | 8.2 |
| 500 | 15710FW | 540 | 8.0 |
| 500 | 16818FW | 543 | 8.6 |
| 500 | 20715FW | 544 | 8.8 |
| 1000 | 12024JT | 1038 | 3.8 |
| 1000 | 22031JT | 1035 | 3.5 |
| 1000 | 24056JT | 1037 | 3.7 |

As seen in the above table, the average Hospira volumes for all tested lots used by MHS, within a nominal bag size, are very consistent, but the overfill varies by bag size. This information can be compared with the statement made by Baxter (Appendix 4). Similarities are noteworthy.

Returning to Table 2, it is now possible to provide a best estimate on the under-dosing. Based on the declared average overfill, the GEMCITABINE prepared by Marchese may be considered to have an added dilution factor of about 7%. For the MHS reconstituted CYCLOPHOSPHAMIDE, the process of first withdrawing 50 mL from the 250 mL bags (total of 270 mL with the overfill) would leave a net volume of about 220 mL in each bag. That is, the 4000 mg CYCLOPHOSPHAMIDE would now be at a volume of 220 mL, which would result in an added dilution factor of about 10%. By translation, this means the best estimated under-dosing for GEMCITABINE and CYCLOPHOSPHAMIDE was about 7% and 10%, respectively.

It may be constructive to consider the Baxter and MHS bulk reconstitution processes further and offer a rather simple process change (Table 2) that would permit MHS to continue to use the Hospira normal saline bags. The revised MHS methodology would be first to draw up the needed normal saline to be added to the GEMCITABINE or CYCLOPHOSPHAMIDE vials. Second, the remaining (i.e., overfill) normal saline volume in the 100 mL and 250 mL bags, respectively, would then be discarded. This would effectively create an “empty bag”. Thereafter, adding the reconstituted/dissolved drugs into these emptied bags would avoid the former overfill dilemma.

Returning to the discovery of the medication incident, a few of the individual hospitals explored the overfill of the MHS bulk reconstituted bags using various techniques. Some of these methods were comparatively crude. Of these efforts, the New Brunswick group used the best method involving bag weights and specific gravity of the contents. This allowed them to identify the volume and product overfill. They concluded a 10.5% overfill for their CYCLOPHOSPHAMIDE bags. This agrees well with the information presented above.

The preceding average estimate regarding the under-dosing should be understood to incorporate a measure of uncertainty (variability). While a technicality, this measure warrants a brief explanation. One source of the variability would be in the saline contents of the bags. That is, all bags are not absolutely identical in contents. It would also include the variability in CYCLOPHOSPHAMIDE or GEMCITABINE content within the vials obtained from the manufacturers. That is, manufacturers are permitted some latitude in the nominal content. For GEMCITABINE, Omega has reported that the content is ±5%. For CYCLOPHOSPHAMIDE, Baxter has declared their international standard to be ±5%, although for the lots supplied to MHS, the Baxter analysis concluded ±1%. Uncertainty also needs to recognize the human variability in delivering volumes via a syringe during the reconstitution step (Thobani and Steward 1992). Nonetheless, none of these sources of variability inherently bias the under-dosing estimate in any fixed direction. Notwithstanding these identified sources of variability, it would be reasonable to conclude that the resulting under-dosing for CYCLOPHOSPHAMIDE would be about 10% and for GEMCITABINE it would be about 7%.

In conclusion, the bulk reconstitution prepared by both Baxter and MHS entailed the use of only Health Canada approved materials. The process used by MHS was different than that used by Baxter. Although there is no evidence of any malicious or deliberate drug-sparing dilution by MHS in preparing its CYCLOPHOSPHAMIDE or GEMCITABINE, it is evident that an inferior bulk reconstitution process was employed by MHS because there was no accompanying process that identified the final volume and thereby the final concentration. The MHS process would have been acceptable if the final concentration in the CYCLOPHOSPHAMIDE or GEMCITABINE bags had been determined and identified on the labels such that the right volume (dose) would be drawn up at the hospitals in Step #4. A failure to reconcile overfill in the process meant that the reconstituted product assumptions at the hospitals were incorrect and an inadequate volume was withdrawn in preparing the patient-specific dose. This led directly to the under-dosing in Step #4.

### Summary Finding #3

There is no evidence of any malicious or deliberate drug-sparing dilution by Marchese Hospital Solutions (MHS) in preparing their bags of CYCLOPHOSPHAMIDE or GEMCITABINE. MHS employed a process in the preparation of the bulk reconstituted CYCLOPHOSPHAMIDE and GEMCITABINE that failed to compensate adequately for an overfill factor in the supplier's normal saline bags. On the basis of the MHS labels on the bags (4000 mg per 100 mL bag for GEMCITABINE; 4000 mg per 200 mL bag for CYCLOPHOSPHAMIDE), the best estimate is that the average actual CYCLOPHOSPHAMIDE concentration was 10% lower than that stated on the label. For GEMCITABINE, the average actual concentration was 7% lower than stated on the label. In the absence of clarifying patient-related instructions by MHS, the hospitals were not aware of the need to adjust doses accordingly to factor in the aforementioned lower concentrations. Thus, the overfill issue led directly to the patient under-dosing for both GEMCITABINE and CYCLOPHOSPHAMIDE.

## c. Treatment Implications in Patients Due to the Incident

In the early 1900s, the famous German chemist Paul Ehrlich set about to develop drugs that would treat infectious diseases. He was the one who coined the term ‘‘chemotherapy’’ and defined it as the use of chemicals to treat disease (DeVita and Chu 2008). While surgery and radiotherapy dominated the field of cancer therapy into the 1960s, it was learned that combination chemotherapy could enhance cure outcomes in patients with various advanced cancers. The latter observation opened up the opportunity to apply drugs in conjunction with surgery and/or radiation treatments to deal with the issue of micrometastases. This was pursued initially in breast cancer patients, and thus the field of adjuvant chemotherapy was born. Combined modality treatment gradually became common clinical practice (Yap, Amlin and de Bono 2013).

The field of cancer treatment is rapidly changing. Many believe personalized medicine is the Holy Grail of cancer chemotherapy, or for that matter any medicinal therapy. Such an approach tailors the treatment plan to each person’s unique clinical, genetic, genomic, biologic, and environmental information. Yet, in the midst of the common, even idealized use of combination therapies and individualized approaches, the key question is what, if any, harm the CYCLOPHOSPHAMIDE and GEMCITABINE under-dosing brought to the patients.

For the adult cancer patients (see Appendix 3) who were under-dosed about 7% with GEMCITABINE and/or 10% with CYCLOPHOSPHAMIDE, further information about their customary treatments might help to clarify the implications. Cancer Care Ontario’s record was reviewed regarding all its provincial treatment programs (including adjuvant, curative, or palliative) involving these two drugs. Of those patients that commonly receive GEMCITABINE, 74% of their treatment plans include the addition of other drugs (combination therapy). For those commonly receiving CYCLOPHOSPHAMIDE, 96% of their treatment plans use a combination of drugs. Taken at face value, this implies that, in the majority of cases, the under-dosing impact does not rest exclusively upon one drug. The probability, therefore, in combination drug therapy, that a single drug factor, at the stated dosing shortfall, has had an overall serious effect is small, although one cannot establish unequivocally that the impact is completely without risk. For GEMCITABINE, the under-dosing bears the possibility of a greater impact in roughly 26% of the patients because it was the single therapy. Yet, for the two under-dosed drugs, GEMCITABINE’s under-dosing (7%) might be considered to lie within a tolerable margin of error ordinarily permitted in therapy (i.e., ±10%).

The above information about the relatively low degree of under-dosing, along with the prevalence of combination drug use, offers a perspective that is compatible with the oncology decisions at the hospitals. The evidence collected at each of the affected institutions showed that medical oncologists generally did not plan any further or more dose-intensive adult treatments upon discovery of the incident. Patients would simply continue with their regular treatment program.

For the pediatric cases, or in those patients (n=30) who received CYCLOPHOSPHAMIDE for treatment of non-cancerous conditions, the impact or compensatory treatments is not known.

## d. Group Purchasing Organization (GPO) and Vendor Relationships

It is clear that the contractual elements and specifications surrounding the agreement between the GPO (Medbuy Corporation) and vendor are pivotal to the under-dosing incident. This critical linkage needs to be understood in the light of the developments surrounding the historical (i.e., incumbent) outsourcing vendor (Baxter), the Ontario Broader Public Sector Procurement Directive, and the eventual switch to the new vendor (Marchese).

Baxter began offering outsourced admixing services within Canada in 1986. Its Central Intravenous Admixture (CIVA) service provided hospitals with parenteral therapies prepared via quality control processes and clean room facilities. Medbuy, in turn, has been in existence since 1989. This national health care Group Purchasing Organization (GPO) uses amalgamated needs in medical supplies, pharmaceuticals, and services to build large purchasing powers and gain the best value from suppliers. In 2008, the GPO negotiated an umbrella contract with Baxter as a CIVA outsourcing supplier of products for its member hospitals. As is evident from the historical record, Baxter had established a prior reputation of providing valuable CIVA services to individual hospitals that was built on understanding the nature of hospital pharmacy and the needed services the vendor could provide.

With the impending expiry of the Baxter contract (2008 to 2011), Medbuy publicly announced its intent to renew the Baxter contract. Marchese objected because it believed it could deliver the service; Marchese indicated that it would like to be considered. Marchese was investigated by Medbuy and found to have a good reputation in providing community services, notably to Community Care Access Centres (CCACs). After investigating its capabilities through its Kitchener-Waterloo facility and attending services, Marchese was considered a potential service provider. In part, this was also based on the broad array of admixture products it was already preparing. These products included most of those that Medbuy was intending for its next contract. Under the Broader Public Sector Accountability Act (BPSA), the GPO needed to open the contract to other providers. The procurement process thereafter led to a request for proposals (RFP), and eventually three organizations presented proposals (Baxter and Marchese from Ontario, and Gentès & Bolduc from Québec). Medbuy used an objective scoring system to evaluate each of the bids. The points-based scoring involved four factors as follows:

- 25 points for the financial cost of the basket of products to be contracted
- 30 points for pharmaceutical/technical criteria (20 evaluation criteria; e.g., staff, training, testing, facility, etc.)
- 30 points for business criteria (11 evaluation criteria; e.g., customer service, order/delivery process, rush order process, etc.)
- 15 points for labels (about 13 evaluation criteria; e.g., bar-coding, font size, colour, etc.)

Thus, of the 100 potential points, the financial element was only 25%. Scoring was done by Medbuy Pharmacy staff and committee members. In this objective scoring, Marchese attained the highest average points and thereby was awarded the contract.

In awarding the contract, a simple statement of the specifications was used for all the approximately 120 products. They were identified in terms of the amount of active ingredient per unit of the product (e.g., GEMCITABINE 4 g in 0.9% sodium chloride injection bag 100 mL/bag). It was assumed this was the only specification needed. Labels (without additional finished product concentrations other than the nominal concentration mentioned above) were approved by its staff and Pharmacy Committee. It was assumed this provided the needed specification and product identity. The GPO and the approval committee did not realize that this simply stated product specification would present unintended consequences.

When MHS began producing the CYCLOPHOSPHAMIDE and GEMCITABINE products, it assumed that the customary nominal concentration (based on the bags containing a nominal volume; e.g., 100 mL, 250 mL, etc., of 0.9% sodium chloride) was adequate even though all bulk reconstituted products for these two products were not intended to be delivered as the entire dose for a single patient.

The root cause of the incident has now been identified. It discloses that there were shortcomings in the transition (i.e., change management) from Baxter to Marchese. Some of this is attributable to assumptions by the GPO and its Pharmacy Committee, failure to accommodate the precise needs of the end-user (pharmacists) in the hospitals, and short-sightedness in creating a seamless transition. Some of this is also attributable to Marchese as it also failed to recognize fully the end-user's needs. That is, it did not factor in the requirement for patient-specific concentration-based doses and the in-hospital procedure in withdrawing a prescribed dose/volume from the bulk reconstitution bags. However one views this development, it is clear that this entire incident underscores significant inadequacies in communication and implementation around specifications, preparing products, and the GPO-vendor handoff that safeguards patient care.

**Summary Finding #4**

Commodity-based large group purchasing contracts which simply bridge the gulf between a manufacturer of a product and a purchaser or an end-user are comparatively straightforward. The commodity is merely transferred in an unchanged form from one location to another. However, a purchasing contract that relies on interpreted services is rather different, as observed in this case with drug product preparation/modifications (e.g., reconstitution). Important factors, including patient risk, were not explicitly considered. It is clear in the present case that shortcomings surfaced within both the GPO and the vendor. The entire incident was preventable. The deficiencies need to be addressed, as will be described later in the recommendations.

# 5. Recommendations

The April 15, 2013 mandate was to conduct a review of the incident and thereafter to "provide recommendations to prevent future incidents of this nature". In a real sense, the incident was about treating patients with compromised doses of two oncology medications. More analytically, it might be about preparing substandard products. This implies that the mandate should address similar potential outcomes that might arise more broadly from non-sterile and sterile preparation practices, at any location.

The information presented in the Observations from the Investigation illustrates the intricacies within the overall system that are associated generally with medications and more specifically the current case of substandard oncology medications. Included in the complexities are:

- The vital and even critical relationships among a GPO, vendor, and hospitals
- The challenging role for pharmacists in preparing products/doses and delivering services to achieve patient-specific medication strategies
- The enlarged responsibilities of pharmacists as presented by the remedial clarification from the MOHLTC, HC and the OCP
- Uncertainties about defining product manufacturing versus compounding
- Jurisdictional oversight questions when products are prepared outside a licensed pharmacy
- The movement of product services across a provincial border.

From the breadth of the above inventory, it is not surprising that various gaps have been observed. While the investigation has centred relatively narrowly on the under-dosing of GEMCITABINE and CYCLOPHOSPHAMIDE, apprehensions have arisen about related professional, institutional, and systemic factors.

The primary concern and accompanying recommendations to be presented are intended primarily to protect patients. Where review observations identified compromised quality/service and/or patient safety, it seems self-evident that shortcomings should be addressed even if the recommendations might extend beyond the immediate oncology case. Watershed occasions like this would be left unsatisfied if such broader, encompassing recommendations were not considered.

The ensuing recommendations will best be understood through the lens of the preceding section that details the observations. The strategy is to begin within the specific GEMCITABINE and CYCLOPHOSPHAMIDE issue. By implication, this means that the first aspect to address is Group Purchasing Organizations and the pharmaceutical service vendors. Thereafter, the broader issue of product preparation is addressed.

## a. The Group Purchasing Organization (GPO)

While there are various stakeholders connected with the incident, the key discovery involved the GPO and the vendor. In the outsourcing that took place, these two are clearly linked. The request for proposal (RFP) that led to Marchese being awarded the contract is a contributing factor. This development led ultimately to the under-dosing with the oncology medications. Therefore, the generic facet of GPOs will be considered first, then the selection and adjudication process for a vendor, thereafter the pharmaceutical preparation service specifications that are needed so that a vendor provides precisely what is required, and finally, some thoughts around new vendors. This concludes with a specific opinion regarding Medbuy and MHS.

The common response that surfaced when the incident unfolded was that the affected hospitals reverted to a complete in-house medication preparation process. It was felt by the hospitals that this action would eliminate uncertainty, ensure a rapid stop-gap solution, and provide some separation from the negative stigma associated with the vendor. Essentially, there was greater confidence in what was done in-house with trusted personnel.

One potential solution to avoiding future oncology admixture mishaps could be to recommend that high-risk services, like the reconstitution of such medications, not be permitted by any outsourced vendor. All similar services would be restricted to hospital or clinical in-house preparation. Such a recommendation would be overly reactionary and could be short-sighted.

It is not known what the economics of hospital in-house services versus outsourced services are. It is also not known objectively whether providing the sterile services in-house actually offers better quality products/services than what is available from an outsourced vendor that prepares them accurately, consistently, conforming to USP <797>, and featuring state-of-the-art facilities. Factors that influence such considerations would include personnel costs, scheduling demands, facility limitations, risks, etc.

Regardless, it appears that hospitals and other clinical institutions continue to face the need to find less costly ways of delivering the same or better services. This challenge will not diminish and the opportunities for solving this challenge remain viable within a model of outsourcing[4].

Additionally, as is evident in this incident, it should be remembered that the problem was not limited to Ontario hospitals. New Brunswick was also affected. That is, a vendor in one part of Canada provided inter-provincial services. In reviewing the GPO's RFP applications, another vendor (in Québec) was also prepared to offer its services. Outsourcing is undoubtedly here to stay; more vendors will likely surface, even from potential off-shore locations, simply because there is an identifiable opportunity, and furthermore that Canada is adjacent to the large US market. It seems that there is a high probability that vendors will seek to expand and offer even more services, especially if economies of scale and excellence can be achieved by such service.

[4] ASHP Guidelines on Outsourcing Sterile Compounding Services

Therefore,

**Recommendation #1:**
Notwithstanding the under-dosing incident, the continued use of Group Purchasing Organizations (GPOs) to negotiate vendor product preparation pharmaceutical services shall not be discouraged. However, improvements are needed in the GPO-based processes.

### *Further Recommendation Comments:*

- The GPO provides distinct benefits by using its members' amalgamated needs in pharmaceutical services to obtain best value for clinics/hospitals.
- The oncology medication incident is a reminder that particular caution is needed when products or services pose an identifiable patient-specific risk.
- Specific improvements within GPO, based services are identified in Recommendations #2 through #4.

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An influencing factor in the GEMCITABINE and CYCLOPHOSPHAMIDE issue was the requirement under the Ontario Broader Public Sector Procurement Directive. This meant that despite a satisfactory track record by the incumbent vendor (Baxter), the Directive and Act (BPSA) required that a transparent, fair, and open process be used in awarding contracts. Furthermore, the Directive identified various requirements in the area of bid submissions and their Evaluation Criteria. It states, for example, that:

*"Competitive procurement documents must clearly outline mandatory, rated, and other criteria that will be used to evaluate submissions, including weight of each criterion"*
and
*"Mandatory criteria (e.g., technical standards) should be kept to a minimum to ensure that no bid is unnecessarily disqualified".*

Interestingly, the above requirements do not forbid the use of specialized or even mandatory criteria, although it could be interpreted that careful justification is needed to avoid prejudicial selection. Regardless, this provision opens the door for unique considerations when high-risk pharmaceutical services are being considered. This aspect warrants attention by GPOs in evaluating proposals.

Therefore,

**Recommendation #2:**
Every Group Purchasing Organization (GPO) shall review its procurement process to ensure that risk for patients is considered an essential evaluation and adjudication criterion when considering proposals.

### *Further Recommendation Comments:*

- The onus for this recommendation shall be upon the GPOs.
- The GPO review shall particularly target sterile compounding procedures wherein contamination, compounding errors, critical dosing, and unsafe practices pose a major risk; segregating high-risk services from more commonplace services, shall be considered in tendered contracts rather than bulking all services regardless of risk.
- Strict adherence to USP <797> shall be required; diligent attention shall be given to aspects that include quality controls, surveillance strategy, testing procedures, risk containment, and both product and facility monitoring.
- Experience by a vendor in delivering risk-prone services shall be considered a factor in evaluating proposals.
- Lastly, the GPO shall consider developing a risk code for products and/or services intended for patient treatment. The code will range from low to high risk. This code could guide GPOs in establishing risk-related evaluation criteria, and in the selection and adjudicating process. The GPO is advised to consult with the Canadian Society of Hospital Pharmacists (CSHP) and the Institute for Safe Medication Practices (ISMP) about developing the risk code.

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It could reasonably be assumed that one of the following two GPO/vendor developments would have averted the incident:

- That the GPO would have provided the new vendor (Marchese) with very explicit, detailed specifications and a specific bulk reconstitution process (like that used by the incumbent vendor). This assumes that the new vendor (Marchese) would have followed this specific product preparation recipe. Regardless, the detailed specifications and the bulk reconstitution process were not presented to the new vendor.
- That the new vendor (MHS), without the specifications noted above, would instinctively have created its GEMCITABINE and CYCLOPHOSPHAMIDE products in the precise way that the incumbent vendor (Baxter) was reconstituting its products. Or, that MHS would have conducted additional finished product testing to identify the actual final fluid volumes and thereby the final concentration of the GEMCITABINE and CYCLOPHOSPHAMIDE in its bulk reconstituted bags. Or, as stated previously, that a different process would have been used that effectively recreated an empty bag approach before bulking the reconstituted drugs. None of these occurred.

It is evident from the above that there was a gap particularly in providing explicit pharmaceutical service requirements to the vendor. Such detailed requirements would seem self-evident for a change to a new vendor wherein a seamless, risk-mitigating transition is essential. The elements in such specifications would logically also include a way of rapidly tracing any issues that could surface regarding materials used in the processing of the products.

Therefore,

**Recommendation #3:**
Every Group Purchasing Organization (GPO) shall develop and adopt a standardized product and/or service specification description that outlines the requirements for contracted sterile or non-sterile pharmaceutical product services.

### *Further Recommendation Comments:*

- A general specification description shall be developed by clinical leaders who routinely use the products or services in the hospitals and/or clinics. That is, the end-users' requirements must be met.
- Additional input regarding the general specification description shall be sought from the Canadian Society of Hospital Pharmacists (CSHP) and the Institute for Safety of Medication Practices (ISMP).
- In the awarding of any vendor-specific compounding, admixture, or manufacturing service, the following minimum details shall be required in the formal contract-specific specification for each pharmaceutical service:
    - The Health Canada approved materials to be used
    - The specified process to be followed like the order of preparation/mixing and the use of equipment or materials (like empty bags) that comprise the final product
    - All specifications about weights and measures
    - All specifications about final product testing, including quality controls to verify the final product
    - The specification for any shelf-life determination; the assigned shelf-life shall accompany any product sent to clinics/hospitals
    - Storage conditions shall accompany any product sent to clinics/hospitals
    - Specifications regarding all important label details from the items above, including the contents that define the product, weights, volumes, concentrations, product bar-coding requirements
    - Instructions to the end-user (e.g., oncology pharmacist) regarding the steps to be used in providing the product or service to the patients.
- An electronic database shall be required of the outsourcing vendor for all its materials, their lot numbers, and expiry dates.
- New vendors bring added risk, and therefore the GPO shall develop a change management plan that shall be exercised whenever a new vendor is selected. This shall include a test with "trial samples":
    - At each clinical institution serviced by the new vendor, the end-user (e.g., oncology pharmacist) that uses the product or service in treating patients shall review and sign off on the acceptability of the "trial sample".
    - Upon formal initiation of the service at the clinical institution, the receipt by the pharmacy of real treatment product(s) or services shall require an acceptance signature that the shipments' specifications have been met.
- The MOHLTC may employ an attestation to confirm that this recommendation has been followed.

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The discovery that a central matter revolved around the GPO and vendors is a signal that, in the interests of safeguarding Ontario's people, the Ministry of Health and Long-Term Care needs to take a more proactive role in this aspect of procurement within both the public and the private segments of patient care. In view of this, the following is recommended:

**Recommendation #4:**
Annually in January, each Group Purchasing Organization (GPO) shall publicize information regarding the contracted pharmaceutical services provided by all its vendors.

### *Further Recommendation Comments:*

- The information shall include contact information for each vendor along with an itemized list of all component non-sterile and sterile pharmaceutical services that have been contracted.
- This recommendation applies to all contracted pharmaceutical patient-related services intended for private and public clinics or hospitals.
- This recommendation applies to all services originating within Ontario or services that are imported into Ontario.
- The MOHLTC shall stipulate the location for such publicized information; it could be within a designated provincial agency or even a location like the Canadian Institute for Health Information. The information shall be readily accessible within the public domain.
- The MOHLTC may employ an attestation to confirm that this recommendation has been followed.

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Lastly, it is important to return specifically to Medbuy and Marchese. Recommendations #2 to #4 already include Medbuy. Recommendation #3 should be instructive to both the GPO and vendor. It stipulates the nature of a relationship that in essence includes the GEMCITABINE and CYCLOPHOSPHAMIDE service products. However, it also magnifies product preparation issues that must be addressed for all MHS products. Functionally, there is no reason why the shortcoming for these products can't be resolved quickly such that there is no uncertainty or misunderstanding at the point of use by the pharmacy/clinicians in the patient care centres. More importantly, that with such clarification and correction, patients will be treated safely and accurately with the MHS outsourced pharmaceutical services.

Therefore,

**Recommendation #5:**
Marchese Hospital Solutions (MHS) shall review and revise its product preparation processes to ensure that all its products meet the specifications required by professionals in treating patients effectively and safely.

### *Further Recommendation Comments:*

- MHS shall contact the end-users (e.g., oncology pharmacists) that employ its service products in treating patients; the product specifications shall be revised as needed to satisfy the requirements.
- The product preparation process shall be modified, where needed, to meet the exacting specifications.
- Importantly, the changes shall eliminate any confusion or misunderstanding regarding products/services designed to deliver an entire prepared dose, a fraction of the product and/or a concentration; the use of automated delivery systems (based on a dose, concentration, volume) shall be accommodated within the changes.

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## b. Manufacturing and Compounding

The recommendations now move to a more careful examination of manufacturing and compounding, with a focus particularly on pharmacy.

Figure 4 displays a gradient that encompasses pharmaceutical manufacturing, compounding and the role of pharmacy within a product preparation continuum. It also displays a zone in which outsourcing vendors offer specialized services that include comparatively high volumes/numbers of sterile and/or non-sterile products for patients.

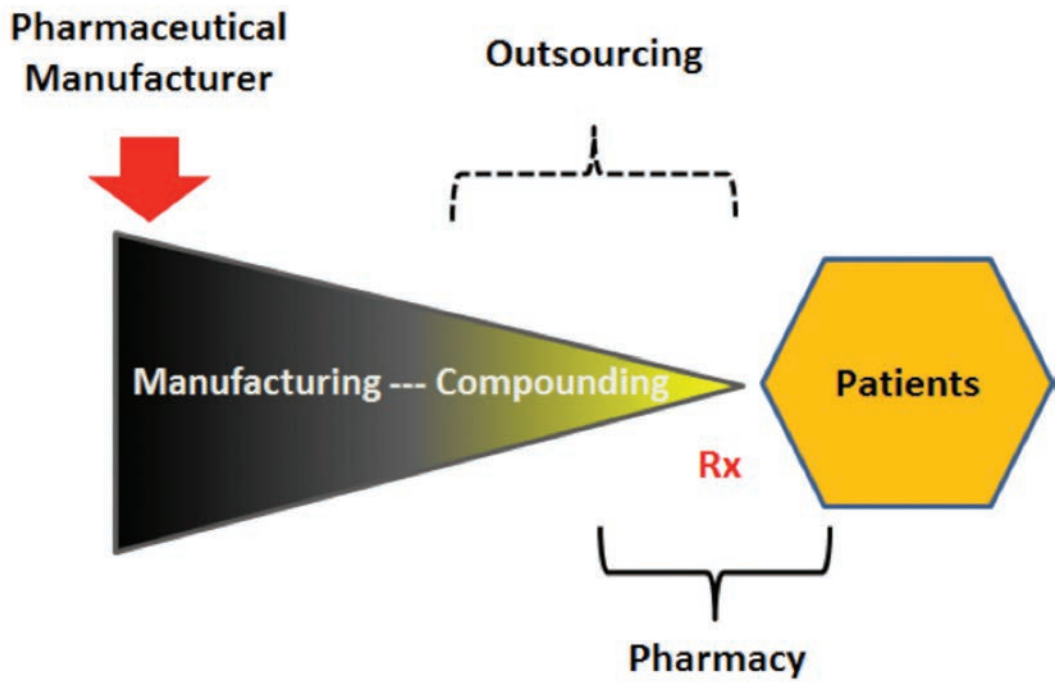


Figure 4: The continuum from pharmaceutical manufacturer to the patient.

A brief historical overview might shed more light on the continuum. Pharmacy presents a long tradition of providing prescribed products for patients. Before the advent of the pharmaceutical industry, pharmacy was almost exclusively engaged in a compounding role. Through a prescription (Rx), a physician inscribed particular active and excipient ingredients and their amounts to formulate a patient-specific product. Eventually, pharmaceutical companies appeared, replacing most of the pharmacists' compounding with mass-produced finished products that could now simply be used, as manufactured, to fill patient prescriptions. Subsequently, pharmacy gradually evolved its professional practice into more of a clinical, patient-oriented role.

The by-product of this change is that compounding has increasingly become dormant, and academic curricula have essentially eliminated this from their Pharmacy programs. Yet, some pharmacies have sought to retain patient-specific product preparation services, sometimes out of historical traditions. Moreover, such services have also been driven partly by specialized patient interests and needs (e.g., inability to swallow customary pharmaceutical products) along with a growing contemporary demand for personalized medicine. Product preparation opportunities have not been restricted to pharmacy. Physicians, dentists, veterinarians, etc., have similarly created

products that satisfy individualized client needs or interests. Lastly, within the continuum, some entrepreneurs have recognized additional possibilities in meeting both product and clinical needs by providing efficient, cost-saving services. Outsourcing has emerged as a relatively large-scale segment of compounding, mixing, and admixing; in many cases this borders on manufacturing. This territory includes both non-sterile and sterile products. The present oncology case illustrates vendors that have provided a Central Intravenous Admixture (CIVA) service to clinics/hospitals. They have specialized in compounded or admixture products delivered in a timely, efficient, and cost-effective way.

Returning to Figure 4 and the product preparation continuum, the following categories of enterprises can be identified:

- Category 1: Pharmaceutical manufacturers
    - They are licensed by Health Canada.
- Category 2: Licensed pharmacies – no compounding
    - They do not compound non-sterile or sterile products.
    - They may contract individual patient-specific product preparation prescriptions to another pharmacy.
    - They are licensed by provincial Colleges of Pharmacy.
- Category 3: Licensed pharmacies – modest compounding
    - They compound relatively small numbers of non-sterile or sterile products.
    - The products are for their patients or contracted (nearby) patients.
    - They are licensed by provincial Colleges of Pharmacy.
- Category 4: Licensed pharmacies – large volume compounding
    - They compound a relatively large number of non-sterile or sterile products.
    - The compounding may be carried out by pharmacists or other personnel like pharmacy technicians.
    - The products may be for their own patients, but they may also serve the needs of patients in various provincial or extra-provincial locations.
    - These are licensed by provincial Colleges of Pharmacy in whichever jurisdiction they are located.
- Category 5: “Outsourcing” businesses – produce varying pharmaceutical, dental, or veterinary products
    - They operate on a scale that approaches manufacturing.
    - They are not a pharmacy nor licensed by provincial Colleges of Pharmacy.
    - The ownership is not restricted to professionals but may include them.
    - They may or may not have pharmacists or pharmacy technicians preparing products.
    - Their business may include products/services to various patient-related organizations (e.g., hospitals), potentially across borders.

In view of the current oncology case and the remedial clarifications initiated by the MOHLTC, HC and the OCP, there initially were various uncertainties that needed rapid attention. This review moreover has afforded an opportune occasion for further consideration and more clarification such that enterprises in the continuum prepare safe and high-quality products for patients. In view of the aforementioned evolution in pharmacy practice, it would be short-sighted to assume that a current degree in Pharmacy and licensure with a College of Pharmacy is a singular assurance that extemporaneous product preparation is safe and of high quality. A licensed pharmacy is inherently no guarantee that product preparation activities within its walls are safe and of high quality. By extension, any specialty outsourcing business, which employs a licensed pharmacist or pharmacy technician, should not be assumed inherently to provide safe product preparation. To ensure that high-quality compounded products are presented to patients, no matter the volume of such a service, consistent, specific standards and operational conditions need to be met by all.

The general principles for such requirements should conform to what is specified for Category 1 pharmaceutical manufacturers. These enterprises must comply with Good Manufacturing Practices (GMP). That is, product preparation shall feature the highest expectations for quality, consistency, product safety and efficacy. For personnel, GMP specifies that any person engaged in the manufacture, processing, packaging, etc., of a drug product shall have education, training, and experience in keeping with the requirements of the assigned functions. With such benchmarks as a foundation, a series of recommendations will be provided that seek to challenge the pharmacy profession to stake more rigid standards, conduct more compliance evaluations, and thereby refine various product preparation practices.

Notwithstanding the existing OCP guidelines on non-sterile and sterile compounding, and the Health Canada Policy (POL-0051), there is a substantial risk to patient safety for extemporaneously prepared products that do not meet the highest quality standards, particularly those associated with sterile compounding. This has been a rallying concern by the (US) ISMP[5]. In view of various incidents highlighted in its newsletter, ISMP has come out strongly advocating sharpened oversight, inspections and adherence to the US Pharmacopeia (USP) standards for both non-sterile (Chapter <795>) and sterile (Chapter <797>) compounding.

Therefore,

**Recommendation #6:**
The Ontario College of Pharmacists (OCP) (and by extension the National Association of Pharmacy Regulatory Authorities [NAPRA]) shall work quickly with Health Canada to define best practices and contemporary objective standards for non-sterile and sterile product preparation within a licensed pharmacy.

[5] http://www.ismp.org/Newsletters/acutecare/showarticle.asp?id=34

### *Further Recommendation Comments:*

- This recommendation is directed at Category #2 to #4 licensed pharmacies.
- For Categories 2 and 3, the patient identity requirement shall be reviewed, including medication records held by a pharmacy; the nature of specific patient identity shall be clarified in extended contractual relationships whether in community pharmacies or via sub-locations within hospitals/clinics.
- In considering the objective standards, these agencies would be highly advised to embrace USP <795> and USP <797>. While this may present conditions that can't easily be met by all, conformity to the standards shall not be based on business suitability but primarily on patient safeguards; consideration may be given for waivers of some of these requirements providing there is legitimate justification. Small volume product preparation pharmacies shall not be permitted lesser standards.
- The agencies are hereby reminded that USP <795> and USP <797> are embraced by the Canadian division of the Professional Compounding Centers of America (PCCA), which provides extra-curricular education and training for many students/graduates.
- Compliance with the objective standards shall be the basis for College inspections; the Colleges and Health Canada shall collaboratively establish inspection protocols and specifications for compliance such that consistency is found for all licensed pharmacies along the product preparation continuum.
- Material records shall be kept by the pharmacy (see Recommendation #7).
- A timeline shall be identified for the completion of the definition of the activities in this recommendation.

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The next accompanying pharmacy recommendation revolves around knowing what materials are being used in the preparation of non-sterile and sterile products. An important concern is that should any contamination or compromised quality be found in any material (active ingredient, excipient, or product storage container), a recall of all affected products would be required. Therefore, searchable/traceable records should be kept, such that all affected products and patients can be found quickly. This should become a norm for all compounded products whether prepared in hospitals (Recommendation #12), licensed pharmacies, or non-pharmacy businesses (Recommendation #10) engaged in non-sterile or sterile product preparation.

Therefore,

**Recommendation #7:**
The Ontario College of Pharmacists (OCP) (and by extension, the National Association of Pharmacy Regulatory Authorities [NAPRA]), shall stipulate specialized electronic material records and label requirements for non-sterile and sterile product preparation within a licensed pharmacy.

### *Further Recommendation Comments:*

- This is directed at Category #2 to #4 licensed pharmacies.
- All non-sterile and sterile product preparation shall include an electronic materials database that lists all ingredients for a product, including their manufacturer, DIN, lot numbers, and expiry date. A certificate of analysis of all materials should be available. Although it is assumed that only Health Canada approved materials shall be permitted in non-sterile and sterile products, all materials shall be of an appropriate identity, purity, and quality suitable for humans; they shall be purchased from reliable sources and properly stored according to manufacturer specifications or USP standards.
- Non-sterile and sterile products prepared within a pharmacy shall have a finished product expiry date.
- All pharmacy labeling shall quickly progress to comprehensive bar-coded identification in keeping with global GS1 standards integration being promoted by Canadian healthcare supply chain partners. For non-sterile and sterile products, this bar-coding shall be connected to the above materials database. In this way, traceability can be assured. Advice from the Institute for Safe Medication Practices (ISMP) should be considered. A timeline shall be set for such bar-coding requirement.

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At the point of this review, it remains unclear how much non-sterile and sterile product preparation takes place on average within pharmacies. There is evidence that some pharmacies are not involved in product preparation, whereas some locations are heavily involved. There is thus a great spectrum of involvement in this practice. While all pharmacies that engage in such extemporaneous compounding should be highly vigilant and careful in providing only the finest quality products, the greatest risk, simply based on volume and patient numbers affected, would be the large volume businesses. It is these that need to be monitored most closely.

Therefore,

**Recommendation #8:**
The Ontario College of Pharmacists (OCP) (and by extension the National Association of Pharmacy Regulatory Authorities [NAPRA]) shall consider a special designation and licence for any licensed pharmacy engaged in large volume non-sterile and sterile product preparation. Such pharmacies shall be inspected annually.

### *Further Recommendation Comments:*

- This is directed at Category 4 licensed pharmacies.
- A metric will need to be developed that assists in identifying this category, whether that is based on a percentage of total pharmacy business or simply product service volume.
- The inherent risk for large volume pharmacy-based production warrants close oversight to avoid any potential miscues that might adversely affect many patients.
- The volume of the business, as mentioned above, shall factor in the relative risk and potential number and types of patients affected.
- Compliance with the preceding standards (Recommendation #6) shall be the basis for annual inspections.
- Consideration may be given for a special display/signage regarding Category #4 pharmacies; this will provide information and assurance for patients.

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The remaining recommendation for licensed pharmacies centres upon the qualifications of personnel that are engaged within a pharmacy in preparing non-sterile and sterile products. For some, the idea of special credentials seems too intrusive; the common perception is that a pharmacy licence qualifies an individual on most professional practice fronts. However, there is already an Ontario special requirement that the administration of injections requires additional training. As stated at the beginning to this Manufacturing and Compounding section, pharmacy has evolved its professional practice into more of a patient-oriented role. The by-product of this change is that compounding has increasingly been left behind and academic curricula have essentially eliminated this from their pharmacy programs. New pharmacists generally do not have compounding skills unless they have gained special extra-curricular training. It is this type of minimal qualification that is needed to promote advanced understanding, skill, and experience in the preparation of non-sterile and sterile products.

Therefore,

**Recommendation #9:**
The Ontario College of Pharmacists (OCP) shall specify credentials beyond education and licensing for personnel engaged in non-sterile and sterile product preparation practices within a licensed pharmacy.

### *Further Recommendation Comments:*

- Only appropriately authorized and qualified personnel shall be involved in the preparation of such products.
- The credentials shall include accredited training programs and official certificates to meet the requirements beyond education such that personnel engaged in product preparation are informed, skilled, and possess specialized training and adequate experience.
- The balance between formal training and experience may recognize previous practice experience in non-sterile and sterile product preparation.

- For the benefit of informing patients, official certificates recognizing the specialized training and/or experience shall be displayed in the pharmacy.
- Consideration should be given to a requirement that each patient receiving a prepared product be given an accompanying product integrity statement by an identified, certified product preparation specialist.

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The preceding section has addressed the matter of safeguarding the public who receive products in a licensed pharmacy that did not originate from a pharmaceutical manufacturer. What about product preparation that falls outside the boundaries of what has been recommended above? Given the array of possibilities regarding the magnitude of business activity, types of products or services offered, and the probability that such items may be crossing provincial or national borders, special precautions are needed to ensure high-quality companies that prepare excellent products and ultimately provide effective and safe treatments.

Therefore,

**Recommendation #10:**
Health Canada shall license all enterprises that function beyond the product preparation permitted within a licensed pharmacy; that is, all product preparation enterprises not within a licensed pharmacy shall be licensed.

## *Further Recommendation Comments:*

- This recommendation applies to Category #5 enterprises.
- This licensing shall also be required of any licensed pharmacy or other enterprise whose product preparation services entail the movement across national or provincial borders.
- The licensing shall be considered for all enterprises that prepare products for humans or animals, whether or not a pharmacist or pharmacy technician is involved.
- The conditions to be met by such product preparation practices shall be molded by the fundamental principles associated with GMP. The degree to which conformity with GMP is required for non-sterile and sterile products shall be defined by Health Canada.
- In conformity with Recommendation #7 for licensed pharmacies, all non-sterile and sterile product preparation shall include an electronic materials database that lists all ingredients for a product, including their manufacturer, DIN, lot numbers, and expiry date. A certificate of analysis of all materials should be available. Although it is assumed that only Health Canada approved materials shall be permitted in non-sterile and sterile products, all materials shall be of an appropriate identity, purity, and quality suitable for humans; they shall be purchased from reliable sources and properly stored according to manufacturer specifications or USP standards. The intent of the detailed records is to provide immediate traceability should the need arise.
- Health Canada licensed product preparation enterprises shall be inspected on a regular (e.g., annual) basis.
- Licensing fees shall be considered commensurate with the volume of business. Such fees can offset the cost of inspections.

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## c. Hospitals, Clinics and Associated Pharmacies

The oncology medication incident exposed the difficulties that can be encountered within hospitals or clinics in identifying patients who have received a particular pharmaceutical product or service. This difficulty may be due to computer systems that are not able to search collaboratively/efficiently within the patient continuum that includes patient identities, admissions, order entries, and treatments. The difficulty may also be exposed by the inadequate labels that surround medication treatments used in hospitals or clinics. This was observed in hospitals and presents a risk that could be particularly problematic should a recall or alert be initiated due to the use of an inappropriate/sub-standard/adulterated pharmaceutical product or any other material used in the preparation of non-sterile or sterile products. High priority needs to be attached to solving these shortcomings in both historical and current patient records.

The following recommendations are directed at the above situations:

**Recommendation #11:**
The Ontario Hospital Association (OHA) shall conduct a formal review/audit to determine the efficiency and traceability of computer-based clinic and hospital records for patients and their treatments, and report the findings to the MOHLTC.

### *Further Recommendation Comments:*

- Tracer techniques could be used to test the systems; the tracer should include searches for drug products, GPO-supplied intravenous diluents, outsourced vendor products, disease types, etc.
- Efficiency should be defined by the permitted longest wait time to collect the information. For example, the retrieval of historical or current information should occur within a time limit of 30 minutes.

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The entire matter of the medication processing and management system within clinics and hospitals needs to be standardized. If the Ontario College of Pharmacists (OCP) is to have greater authority within the clinic/hospital environments, it would allow for a consistent accreditation process across the continuum of pharmacy facilities. Inspection is the primary tool for OCP accreditation and provides for a much more detailed review of pharmacy operation across a full spectrum of activities with specific criteria. Inspection by OCP, as recommended earlier for non-sterile and sterile products, would allow for the consideration of production, distributive, and cognitive aspects of pharmacy operations. This would include a perspective of legislation, scope of practice, and standards of practice specific to this profession. Hospital accreditation does not utilize the same lens, but rather, selects specific aspects of pharmacy practice and evaluates them against the identified required organizational practices (ROPs), such as medication reconciliation. Frequently this is viewed as an activity relegated separately within hospitals or community pharmacy. Yet, the interface between hospital and community care is one of the most challenging parts of our health care system, and medication information and communications between hospital and community pharmacy should be a major area of focus. The inspections by OCP can also address the processes for medication reconciliation on patient admission and discharge. When both community and hospital pharmacies go through the College led processes, the College would add a specific ability to motivate practice and processes beyond what the voluntary general

hospital accreditation could do. Clearly, this could facilitate a new effort in medication controls, management, and reconciliation.

There are many pharmacy operations that are not included in the hospital ROPs, yet are still vitally important to patient safety. Hospital accreditation, which would continue even if OCP oversight was introduced, looks at pharmacy practice as being embedded within the health system; both perspectives are necessary and not exclusive of one another.

OCP oversight would also allow for an inspection schedule that could be more frequent than hospital inspections and could be completed on an ad hoc or as needed basis. OCP inspections also would evaluate against minimally acceptable standards, rather than best practice, and therefore the consequences of non-compliance would be more impactful. A hospital can achieve accreditation overall as an organization, yet have deficiencies within pharmacy operations for which there may not be a mandate to improve. OCP oversight would allow for mandatory compliance of operations that put patient safety at risk.

Therefore,

**Recommendation #12:**
The Ontario College of Pharmacists (OCP) shall license all pharmacies operating within Ontario's clinics or hospitals.

## *Further Recommendation Comments:*

- This step of standardizing the pharmacy operations and practices brings the greatest potential patient benefits and reduces some of the identified medication management risks. It also implies that the previous recommendations targeted at licensed community pharmacies need to be adopted for clinic and hospital pharmacies. That is:
    - The category of drug product preparation activity (high vs. low volume).
    - The OCP shall work quickly with Health Canada to define those non-sterile and sterile product preparation distinctions that shall be considered for a licensed clinic or hospital pharmacy.
    - The OCP shall require a recognized standard of practice for non-sterile and sterile product preparation within a hospital pharmacy. Particularly, as identified earlier, the OCP would be advised to embrace the standards of USP <795> and USP <797> and require this standard for clinics and hospitals. Waivers of some of these requirements could be permitted with justification.
    - The OCP shall stipulate specialized electronic records and label requirements for non-sterile and sterile product preparation within a hospital pharmacy. As elaborated earlier, such preparation shall include an electronic materials database that lists all ingredients for a product, including their manufacturer, DIN, lot numbers, and expiry dates for both materials and the finished prepared products.
    - A timeline shall be set for all hospital pharmacy labeling to comply with comprehensive bar-coded identification for all products in all patients. For non-sterile and sterile products, this bar-coding should be connected to the above materials database. In this way, traceability could be assured. Advice from the Canadian Society of Hospital Pharmacists (CSHP) and the Institute for Safe Medication Practices (ISMP) should be considered.

## d. Patients Receiving Under-dosed GEMCITABINE or CYCLOPHOSPHAMIDE

The preceding recommendations have focused on the process of group purchasing, vendors, materials/products, and institutions. These are the primary components to address in seeking to improve future quality of products, services, and operations, and to offer confidence that a similar incident will not take place again.

The estimated impact on patients of the under-dosing with GEMCITABINE and CYCLOPHOSPHAMIDE has been addressed previously in Section 4c. Is this estimation adequate? Unfortunately, there is no known objective research and peer-reviewed literature regarding the consequence of 7% and 10% under-dosing for GEMCITABINE and CYCLOPHOSPHAMIDE, respectively, upon patients. Furthermore, little general information is available regarding the effects of unintended chemotherapy under-dosing in patients. As a result, there is no readily available information that can be consulted to shed more light on the incident and no further recommendations to present.

The only additional option has been to seek a further independent academic/clinical perspective from a distinguished and experienced medical oncologist outside Ontario. Such an individual needs to have broad recognized credentials in scientific and clinical medicine and be very familiar with the types of treatments that were represented among the 1202 affected patients.

Being an independent reviewer brings freedom while posing some limitations. As an academically oriented investigator of the current incident, I felt the above option could enlighten my aforementioned estimation and possibly offer instructive new insights on the incident. The perspective might even become a harbinger of future research that could illuminate the problem. To that end, I have requested such a viewpoint, but at this point the information is not yet available. Such eventual information should, however, not be considered a missing component of this report. When I gain the further oncology perspective, it will be studied, considered, and shared as deemed appropriate, independently.

# 6. Conclusion

This review conducted an investigation into the oncology medication under-dosing that surfaced in four Ontario hospitals and within New Brunswick. Despite the intrusive, troubling nature of this development, many clinicians and other hospital personnel worked admirably in quickly meeting and largely overcoming this challenge. Evidence supports the view that the hospitals performed well in this crisis. The decisive steps taken, whether in hospitals or through provincial or national stakeholder agencies, demonstrated commendable crisis-stemming leadership.

The review has addressed all aspects of the mandate. It investigated the incident and uncovered the root cause of the under-dosing. It thereafter assembled a variety of recommendations that are not restricted to the oncology medications prepared by an outsourcing vendor. They are intended more broadly to prevent future incidents of a similar nature and to mitigate identifiable risks in the extended realm of non-sterile and sterile product preparation within licensed pharmacies and other enterprises. It is this call for improvements that should sharpen patient treatment safeguards.

# 7. Acknowledgements

It is with much gratitude that I acknowledge the assistance of various individuals and organizations that made the work of this review possible.

First, although this investigation has been independent, the Ministry of Health and Long-Term Care was exceptionally helpful in facilitating my workplan, scheduling, contacts, and visits. Valuable advice was also gained when questions arose. The working group, established by the ministry, provided important insights into the various facets of professional, structural, and regulatory oversight associated with the oncology medication incident.

Secondly, the diverse organizations that were visited and interviewed to learn about the incident, including its causes and implications, were uniformly cooperative and generous in sharing evidence and information. Alphabetically, they include:

- Baxter Corporation
- Canadian Division of the Professional Compounding Centres of America (PCCA)
- Canadian Society of Hospital Pharmacists (CSHP)
- Cancer Care Ontario (CCO)
- Health Canada (HC)
- Hospira
- Institute for Safe Medication Practices (ISMP)
- Lakeridge Health
- London Health Sciences Centre
- Marchese Hospital Solutions (MHS)
- Medbuy
- New Brunswick, Saint John Regional Hospital and Horizon Health Network
- Omega Laboratories Ltd.
- Ontario College of Pharmacists (OCP)
- Ontario Pharmacists Association (OPA)
- Peterborough Regional Health Centre
- Windsor Regional Hospital

Lastly, I wish to acknowledge and recognize in particular the numerous patients who faced the emotional impact of the incident. I humbly trust that my efforts in uncovering the cause of the under-dosing, in exploring various particulars around this issue, and providing recommendations will serve to heighten safeguards for both non-sterile and sterile product preparation throughout the health care community. It is my hope that this will offer encouragement and greater confidence in such medications.

# 8. References

Note: These references are not comprehensive, where introduced, but simply illustrate published reports that support the statements.


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# 9. Appendices

## Appendix 1: Abbreviated Biographical Sketch for Jake J. Thiessen, Ph.D.

- Education: B.Sc. (Pharm): University of Manitoba; M.Sc.: University of Manitoba; Ph.D.: University of California, San Francisco
- A former Professor, Associate Dean, and current Professor Emeritus at the Leslie Dan Faculty of Pharmacy, University of Toronto. Following 33 years at the University of Toronto, 6 years were spent at the University of Waterloo (UW) where the appointment and strategic responsibility led to the development of a new Health Sciences Campus and Canada's 10th School of Pharmacy.
- Qualifications and insights have been gained from wide-ranging experiences in professional education, research methodologies, pharmaceuticals, the pharmaceutical industry, medication supply chain and patient care through an academic career of about 40 years.
- Specialized in pharmacokinetics and pharmacodynamics, which basically describe quantitatively those forces that affect how the body handles medicines and how medicines affect the body. The dynamic of these two areas influences strategies around patient treatment regimen in all disease states. Research collaborations included some years working with medical oncologists and basic scientists at Princess Margaret Hospital. In more recent years, the UW research with scientists in cognate fields explored a special region of light and its illuminating benefits in the pharmaceutical and medical fields. This led to the formation of a start-up company (Verisanté) that is traded on the TSX Venture Exchange. The first product (Aura™) is a revolutionary technology allowing skin irregularities to be scanned and thereby assist in the early diagnosis of skin cancer. Broad experience has been gained through international projects in regions/countries like the Caribbean, Nigeria, Saudi Arabia, Sudan and Taiwan; the role of President of the Canadian Council for the Accreditation of Pharmacy Programs; Chair of the Drug Quality and Therapeutics Committee of the Ontario Ministry of Health; and Chair of Health Canada's Scientific Advisory Committee on Bioavailability and Bioequivalence. Currently serving as Health Canada's Chair for the Scientific Advisory Committee on Pharmaceutical Sciences and Clinical Pharmacology.
- The specific interest in this oncology project arose from the aforementioned research associations in medical oncology, a father who passed away prematurely from cancer, and two sisters-in-law who also succumbed to the disease.

## Appendix 2: Investigation Schedule for Initial Visits (V) and Conference Calls (C)*

| Date | Nature | Stakeholder |
|---|---|---|
| 17-4-2013 | V | Peterborough Regional Health Centre |
| 17-4-2013 | V | Lakeridge Health |
| 18-4-2013 | V | London Health Sciences Centre |
| 19-4-2013 | V | Windsor Regional Hospital |
| 22-4-2013 | V | Cancer Care Ontario (CCO) |
| 23-4-2013 | V | Ontario College of Pharmacists |
| 24-4-2013 | C | New Brunswick, Saint John Regional Hospital and Horizon Health Network |
| 24-4-2013 | C | Health Canada |
| 25-4-2013 | V | Marchese Hospital Solutions |
| 7-5-2013 | C | Hospira (Diluent supplier) |
| 9-5-2013 | C | Institute for Safe Medication Practices |
| 10-5-2013 | C | Canadian Society of Hospital Pharmacists |
| 13-5-2013 | C | Omega Laboratories Ltd. (GEMCITABINE source) |
| 16-5-2013 | C | Ontario Pharmacists Association |
| 17-5-2013 | C | CCO – future implications |
| 24-5-2013 | C | Medbuy |
| 6-6-2013 | V | Baxter Corporation (Previous vendor; CYCLOPHOSPHAMIDE source) |
| 6-6-2013 | V | Professional Compounding Centers of America – London, Ontario |
| 7-6-2013 | V | Medbuy |

* Various of these stakeholders have been subsequently contacted on more than one occasion to re-investigate the evidence or discuss the issues further.

## Appendix 3: A Summary of Patient Numbers Affected by the CYCLOPHOSPHAMIDE (C) and GEMCITABINE (G) Under-Dosing; Treatments Were for Cancer or Other Conditions

| Location | Medications | | | Category of Patients | | Conditions | |
|---|---|---|---|---|---|---|---|
| | C | G | C+G | Pediatric | Adult | Cancer | Other |
| Peterborough | | 1 | | | 1 | 1 | |
| Lakeridge | 14 | 23 | | | 37 | 37 | |
| London Health Sciences Centre | 520 | 167 | 4 | 40 | 651 | 669 | 22 |
| Windsor | 290 | | | | 290 | 290 | |
| New Brunswick | 183 | | | | 183 | 175 | 8 |
| **Totals** | **1007** | **191** | **4** | **40** | **1162** | **1172** | **30** |

# Appendix 4: Information from Baxter Regarding Overfill for Various Fluid Bags

January 7, 2013

Baxter

Dear Valued Customer:

Thank you for your interest in the fill volumes for Baxter Canada products. Please reference the specifications by bag size below. The excess volume is aligned with USP standards to achieve delivery of the labeled contents.

| Solution Bag Size (mL) | Manufacturing Fill Specifications (mL) |
|---|---|
| 25 | 30 ± 3 |
| 50 | 58 ± 5 |
| 50 Pharmaceutical | 54.2 + 3.0<br>54.2 – 2.2 |
| 50 Mini-Bag Plus | 58 ± 5 |
| 100 | 110 ± 5 |
| 100 Mini-Bag Plus | 110 ± 5 |
| 250 | 280 ± 15 |
| 250 Mini-Bag Plus | 275 ± 10 |
| 500 | 547.5 ± 17.5 |
| 1,000 | 1050 ± 20 |
| 1500/2000 (Twin Bag) | 1565 ± 27 |
| 2000 (Single Bag) | 2080 ± 40 |
| 2000 (Twin Bag) | 2065 + 55<br>2065 – 25 |
| 2500/3000 | 2570 + 70<br>2570 – 30 |
| 3000 | 3080 – 30<br>3080 + 70 |
| 3000 (TIV) | 3080 ± 50 |
| 5000 | 5120 – 45<br>5120 + 105 |

# Appendix 5: Announced Regulatory Changes by the MOHLTC and the OCP

MOHLTC: Announcement Associated with Changes to Regulation 965 under the Public Hospitals Act

May 15, 2013 10:30 a.m.
Ministry of Health and Long-Term Care

Ontario is protecting patients by strengthening the oversight and safety of drugs that are purchased or obtained by hospitals, including chemotherapy drugs.

The new Ontario government is fulfilling its commitment to improve provincial oversight and safety with respect to the province's drug supply system by enacting regulations, effective today, that will:

- Ensure hospitals purchase drugs only from accredited, licensed or otherwise approved suppliers
- Give the Ontario College of Pharmacists the responsibility to inspect drug preparation premises where pharmacists and pharmacy technicians practice

The government has amended Regulation 965 under the Public Hospitals Act to only allow hospitals to purchase or obtain drugs from certain entities including:

- An accredited pharmacy under Ontario's Drug and Pharmacies Regulation Act
- A person licenced under the federal Food and Drugs Act
- An accredited pharmacy in another Canadian jurisdiction
- A drug preparation premises that passes an inspection by the Ontario College of Pharmacists
- A wholesaler who has bought the drug from a regulated entity (as above)
- A corporation that procures products on behalf of a hospital and has procured from a regulated entity (as above)
- The Government of Ontario or the Government of Canada
- Another Ontario hospital
- A person conducting a clinical trial or named in a letter of authorization under the Food and Drugs Act
- Other situations provided under the regulation

OCP: Regulation and bylaw changes to Ontario Regulation 202/94

May 10, 2013

1. Ontario Regulation 202/94 is amended by adding the following Part:
PART IX INSPECTION OF DRUG PREPARATION PREMISES TEMPORAL APPLICATION

52. This Part applies to the College and members as of the day that it comes into force, except that,
(a) sections 54, 55, 56, 59 and 60 apply as of 90 days from the day that this Part comes into force; and
(b) the requirements in subsection 57 (1) and section 58 apply as of 30 days from the day that this Part comes into force.

INTERPRETATION

53. (1) In this Part,
"designated member" means,
(a) the member designated for a drug preparation premises in accordance with section 58, or
(b) where only one member engages in or supervises drug preparation activities at or in connection with a drug preparation premises, that member;
"drug" means a substance or a preparation containing a substance referred to in clauses (a) to (d) of the definition of "drug" in subsection 1 (1) of the Drug and Pharmacies Regulation Act, but does not include,
(a) a substance or preparation referred to in those clauses that is manufactured, sold or represented for use in animals or fowl, or
(b) a substance or preparation referred to in clause (e), (f), (g), (h) or (i) of that definition;
"drug preparation activities" means 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;
"drug preparation premises" means any place where a member 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 licence 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;
"inspector" means a person appointed by the College to carry out an inspection on behalf of the College;
"supervise" means to supervise either directly or indirectly.

(2) Anything that may be done by the College under this Part may be done by the Council or by a committee established under clause 94 (1) (i) of the Health Professions Procedural Code.

INSPECTION

54. (1) All drug preparation premises are subject to inspection by the College in accordance with this Part.

(2) In carrying out an inspection of a drug preparation premises under subsection (1), the College may also require any or all of the following:
1. Inspection, examination or testing regarding any equipment, instrument, materials or any other thing that may be used in the drug preparation premises.
2. Examination and copying of books, accounts, reports, records or similar documents that are, in the opinion of the College, relevant to the member's practice with respect to the drug preparation activities at or in connection with the drug preparation premises.
3. Inquiries or questions to be answered by the member that are relevant to the member's practice with respect to the drug preparation activities at or in connection with the drug preparation premises.
4. Direct observation of a member in his or her practice with respect to drug preparation activities at or in connection with the drug preparation premises.

55. An inspector may, on the production of information identifying him or her as an inspector, enter and have access to any drug preparation premises at reasonable times and may inspect the drug preparation premises and do any of the things mentioned in subsection 54 (2) on behalf of the College.

56. (1) It is the duty of every member engaging in or supervising drug preparation activities at or in connection with drug preparation premises that are subject to an inspection to,
(a) submit to an inspection of the drug preparation premises in accordance with this Part;
(b) promptly answer a question or comply with a requirement of the inspector that is relevant to an inspection under this Part; and
(c) co-operate fully with the College and the inspector who is conducting an inspection of a drug preparation premises in accordance with this Part.

(2) A member shall not engage in or supervise drug preparation activities at or in connection with a drug preparation premises where an inspector has been denied entry or access.

57. (1) No member shall commence engaging in or supervising drug preparation activities at or in connection with drug preparation premises unless the member has previously given notice in writing to the College in accordance with subsection (5) of the member's intention to do so.

(2) Where a member has provided notice in writing to the College in accordance with subsection (1) and the drug preparation premises have not passed an inspection or passed an inspection with conditions within the previous five years, the College shall ensure that an inspection of the drug preparation premises is performed within 60 days from the day that the College receives the member's notice or 150 days from the day this Part comes into force, whichever is later.

(3) A member who engages in or supervises drug preparation activities at or in connection with a drug preparation premises as of the day that is 30 days from the day this Part comes into force shall give notice in writing to the College in accordance with subsection (5) within 90 days from the day this Part comes into force.

(4) The College shall ensure that an inspection of the drug preparation premises with respect to which a member gives notice under subsection (3) is performed within 150 days from the day this Part comes into force.

(5) The notice required in subsections (1) and (3) shall include the following information, submitted in the form and manner required by the College:
1. The full name of the member giving the notice and the full name of the individual or corporation who is the owner or occupier of the drug preparation premises, if he or she is not the member who is required to give notice under this section.
2. The full address of the drug preparation premises.
3. The date when the member first began engaging in or supervising drug preparation activities at or in connection with the drug preparation premises or the proposed date when the member intends to begin engaging in or supervising drug preparation activities at or in connection with the drug preparation premises.
4. Any other information the College requires that is relevant to an inspection of the drug preparation premises conducted under this Part.

58. Where two or more members engage in or supervise drug preparation activities at or in connection with a drug preparation premises, the members shall designate a member as the designated member for the drug preparation premises, and shall immediately notify the College of the designated member's identity.

59. All drug preparation premises are subject to an inspection by the College once every five years after the initial inspection of the premises or more often if, in the opinion of the College, it is necessary or advisable to do so.

60. (1) After an inspection of a drug preparation premises, the College shall determine, in accordance with the accepted standards of practice, whether the drug preparation premises pass, pass with conditions or fail.

(2) In determining whether drug preparation premises pass, pass with conditions or fail an inspection, the College may consider,
(a) the inspection results provided to the College by the inspector;
(b) information provided by one or more members engaging in or supervising drug preparation activities at or in connection with the drug preparation premises respecting the inspection, including the answers given by them in response to inquiries or questions asked by the inspector;
(c) the information contained in a notice given by a member under subsection 57 (1) or (3);
(d) any submissions made by the member or members engaging in or supervising drug preparation activities at or in connection with the drug preparation premises that are relevant to the inspection; and
(e) any other information that is directly relevant to the inspection of the drug preparation premises conducted under this Part.

(3) The College shall deliver a report, in writing and in accordance with section 39 of the Regulated Health Professions Act, 1991, to the individual or corporation that is the owner or occupier of the drug preparation premises and to the designated member for the drug preparation premises, within a reasonable time after the inspection is completed.

(4) Any report made by the College respecting an inspection of drug preparation premises where a member is engaging in or in respect of which the member is supervising drug preparation activities shall make a finding that the drug preparation premises passed, passed with conditions or failed the inspection and shall provide reasons where the drug preparation premises passed with conditions or failed the inspection.

(5) Any report made by the College that finds that drug preparation premises failed an inspection or passed with conditions is effective on the day that it is received, in accordance with section 39 of the Regulated Health Professions Act, 1991, by the designated member for the drug preparation premises.

(6) The designated member who receives a report made by the College that finds that a drug preparation premises failed an inspection or passed with conditions shall promptly provide copies of the report to all members engaging in or supervising drug preparation activities at or in connection with the drug preparation premises.

(7) A member shall not engage in or supervise drug preparation activities at or in connection with a drug preparation premises that fail an inspection until,
(a) the College delivers a report indicating that the drug preparation premises passed a subsequent inspection, or passed with conditions; or
(b) after considering submissions under subsection (9), the College substitutes a finding that the drug preparation premises pass or pass with conditions.

(8) A member shall not engage in or supervise drug preparation activities at or in connection with drug preparation premises that pass an inspection with conditions except in accordance with the conditions set out in the report until,
(a) the College delivers a report indicating that the drug preparation premises passed a subsequent inspection; or
(b) after considering submissions under subsection (9), the College substitutes a finding that the drug preparation premises pass.

(9) A member may make submissions in writing to the College within 14 days from the date on which a report made by the College that finds that the drug preparation premises passed with conditions or failed the inspection becomes effective in accordance with subsection (5).

(10) The College may or may not elect to reinspect the drug preparation premises after receiving a member's submissions, but no more than 60 days after a member provides his or her submissions, the College shall do one or more of the following:
1. Confirm its finding that the drug preparation premises failed the inspection or passed with conditions.
2. Make a report and find that the drug preparation premises passed with conditions.
3. Make a report and find that the drug preparation premises passed the inspection.

(11) Drug preparation premises that fail an inspection or pass with conditions may be subject to one or more further inspections within a reasonable time after the College delivers its report, at the request of a member, any other person to whom the College gave the report, or at any time at the discretion of the College.

(12) Where, as a result of an inspection carried out under this Part, a report made by the College finds that a member's knowledge, skill or judgment is unsatisfactory, the College may direct the Registrar to refer the report to the Quality Assurance Committee.

(13) Where, as a result of an inspection carried out under this Part, a report made by the College finds that a member may have committed an act of professional misconduct or may be incompetent or incapacitated, the College may direct the Registrar to refer the report to the Inquiries, Complaints and Reports Committee.

Commencement
2. This Regulation comes into force on the day it is filed.

Made by:
THE ONTARIO COLLEGE OF PHARMACISTS:
CHRISTOPHER LEUNG
President
MARSHALL MOLESCHI
Registrar
Date made: May 10, 2013.

Bylaw Amendments and Additions as Approved
Article 1
1.1.22A "Drug Preparation Premises" means Drug Preparation Premises as defined in Part IX of the Pharmacy Act Regulations

Article 7
7.3.6 Drug Preparation Premises Committee
7.7A Appointment of Drug Preparation Premises Committee. Upon the coming into force of Part IX of the Pharmacy Act Regulations, the Drug Preparation Premises Committee shall be formed. The initial appointments to the Drug Preparation Premises Committee shall be for a term that expires at the first regular meeting of Council after the next annual August election. Thereafter, the Drug Preparation Premises Committee shall be formed at the first regular meeting of Council after each annual August election and appointments to it shall be in accordance with Article 7.6.

Article 8
8.28 Composition of the Drug Preparation Premises Committee. The Drug Preparation Premises Committee shall be composed of the same members as the Accreditation Committee. The Chair of the Accreditation Committee shall be the Chair of the Drug Preparation Premises Committee.
8.29 Duties of the Drug Preparation Premises Committee. The Drug Preparation Premises Committee shall:
8.29.1 administer and govern the College's Drug Preparation Premises inspection program in accordance with Part IX of the Pharmacy Act Regulations;
8.29.2 deal with any other matters concerning the inspection of Drug Preparation Premises as directed by the Council.

Article 10

10.5A Inspectors for the Purposes of Inspecting Drug Preparation Premises. The Registrar may appoint inspectors for the purposes of Part IX of the Pharmacy Act Regulations. Inspectors so appointed shall have such authority and shall perform such duties as are set out in Part IX of the Pharmacy Act Regulations.

Article 11

11.5A Additional Information to be kept in Register – Drug Preparation Premises. The following additional information referable to Drug Preparation Premises shall be kept in the Register, and is designated as public pursuant to subsection 23(5) of the Code:

11.5A.1 The outcome and/or status of inspections of Drug Preparation Premises (including conditions and/or reasons for fail results) carried out under Part IX of the Pharmacy Act Regulations, including the relevant date.

Article 13–Member Fees

13.6.3 The fee for the inspection of a Drug Preparation Premises pursuant to Part IX of the Pharmacy Act Regulations, including all activities related to the inspection, shall be $2,500.00 plus applicable taxes, and shall be payable, jointly and severally, by those Members who engage in, or supervise, drug preparation activities at the Drug Preparation Premises.

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