Cancer Care Ontario

Cancer Care Ontario Beyond-Use Date Recommendations Report

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Beyond-Use Date Mitigation Strategy Working Group

Peter Anglin, Regional Quality Lead & Head of Medical Oncology, Southlake Regional Health Centre

Veronique Briggs, Pharmacy Director, Kingston Health Sciences Centre

Flay Charbonneau, Pharmacy Manager, Sunnybrook Health Sciences Centre

Ally Dhalla, Pharmacy Manager, London Health Sciences Centre

Andrea Docherty, Regional Director, Thunder Bay Regional Health Sciences Centre

Anna Granic, Oncology Lead Pharmacist, Grand River Hospital

Jin Huh, Senior Director, Pharmacy, University Health Network

Jiten Jani, Pharmacy Manager, St. Joseph's Health Centre

Alexander Kuo, Pharmacy Manager, The Ottawa Hospital

Sharon Meeke, Pharmacy Manager, Hamilton Health Sciences

Ferid Rashid, Pharmacist, Oncology Services, Halton Healthcare

Amarjit Suri, Pharmacist, Royal Victoria Regional Health Centre

Karina Teterycz, Interim Pharmacy Coordinator, London Health Sciences Centre

Laura Wilcock, Pharmacy Manager, Lakeridge Health

Samantha Wright, Pharmacy Technician, The Ottawa Hospital

Leta Forbes (co-chair), Provincial Head, Systemic Treatment Program, Cancer Care Ontario

Ron Fung (co-chair), Pharmacist, Systemic Treatment Program, Cancer Care Ontario

Daniela Gallo-Hershberg, Group Manager, Systemic Treatment Program, Cancer Care Ontario

Erin Redwood, Group Manager, Clinical Quality Improvement, Ontario Palliative Care Network, Primary Care & Survivorship, Cancer Care Ontario

Kathy Vu, Clinical Lead – Safety Initiatives, Systemic Treatment Program, Cancer Care Ontario

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Cancer Care Ontario Beyond-Use Date Recommendations Report

Summary

- Closed-system drug-transfer devices may be used with single-dose vials to extend the current beyond-use date of 6 hours, if supported by facility-level sterility testing, but should not exceed 7 days.
- A strategy of dose rounding may be used to reduce drug wastage associated with single-dose vials.
- Extending the beyond-use date of single-dose vials should only be implemented where supported by facility-level sterility testing.
- Automated robotic dispensing units may be used to extend the beyond-use date of single-dose vials if local testing consistently demonstrates ongoing sterility under the specified storage conditions.

Background/Introduction

The National Association of Pharmacy Regulatory Authorities (NAPRA) released their Model Standards for Pharmacy Compounding of Non-hazardous Sterile Preparations in November 2015 (revised November 2016) and their Model Standards for Pharmacy Compounding of Hazardous Sterile Preparations in September 2016 (revised November 2016). Current pharmacy practice for the preparation of hazardous and non-hazardous sterile products in Canada includes many patient safety and quality assurance requirements. The mandate of the NAPRA Model Standards is to inform pharmacy personnel involved in the compounding of hazardous and non-hazardous sterile preparations with the standards necessary to evaluate their practice, develop service-related procedures, and implement appropriate quality controls, with a view to set high standards for the overall quality and safety of sterile preparations. The new Model Standards include an on-site quality assurance program, increased system oversight, beyond-use dates (BUD) and recall procedures, among others. In September 2016, the Ontario College of Pharmacists adopted the NAPRA Model Standards for Pharmacy Compounding of Hazardous Sterile Preparations and the NAPRA Model Standards for Pharmacy Compounding of Non-hazardous Sterile Preparations as the standards for sterile compounding in Ontario with implementation by January 1, 2019.

BUD is defined as the date and time after which a drug or compounded sterile preparation (CSP) cannot be used and should be discarded. The NAPRA Model Standards specify that the BUD for CSPs must not exceed the earliest of the dates established by two criteria: expiration date based on the chemical and physical stability according to reference texts, and storage time related to risk of microbial contamination. For hazardous and non-hazardous drugs provided as single-dose vials, the BUD of the vial, once punctured, according to the NAPRA Model Standards is 6 hours (when maintained in an International Organization for Standardization (ISO) Class 5 air quality environment within a containment primary engineering control (C-PEC) (e.g. a biological safety cabinet)). This may represent a significant change in practice for many Systemic Treatment facilities in Ontario as BUD has traditionally been based on chemical and physical stability, which may provide a longer expiration date upon initial vial puncture – up to 30 days in some cases, based on local best practice. Financial modelling by Cancer Care Ontario suggests that this drug wastage due to BUD adoption as per the NAPRA Model Standards for single-dose vials may result in an annual increased cost of $13 to $26M to the provincial cancer drug budget incurred by hospitals and/or cancer centres.

To address the drug waste issue related to BUD implementation as per the NAPRA Model Standards, a BUD Mitigation Strategy Working Group was created and led by the Systemic Treatment Program at Cancer Care Ontario. Membership of the group comprised medical oncologists/hematologists, regional directors, pharmacy leadership, pharmacists, pharmacy technicians and representatives from Cancer Care Ontario. The primary

objective of the Working Group was to develop a Recommendations Report which complies with the NAPRA Model Standards for BUD and provides potential strategies to minimize wastage due to single-dose vials. This Recommendations Report focused on four key areas with potential for the greatest system impact: closed-system drug-transfer devices, dose rounding, facility-level sterility testing, and automated robotic dispensing units. The Working Group members were in agreement that mitigation strategies focused on extending BUD should be limited to single-dose vials, and not CSPs. As such, all references to implementation of the NAPRA Model Standards with respect to BUD in this Report are made only in the context of single-dose vials.

It should be noted that general drug waste not related to BUD was considered out of scope for this Working Group, and that drug waste is not eligible for funding through the Provincial Drug Reimbursement Programs (PDRP) Unit or any other Cancer Care Ontario program.

Closed-System Drug-Transfer Devices (CSTDs)

Summary of Key Published Evidence

Multiple studies have shown the viability of CSTDs for maintaining sterility for up to 7 days. De Prijck *et al*[1] published a study evaluating the susceptibility to microbial contamination among four different CSTDs after inoculating the stoppers of the vials. Of the CSTDs tested, the authors determined that the PhaSeal™ system was the most effective in preventing contamination after repeated entries out of the vials using each device. Additional studies conducted by McMichael *et al*[2] and Carey *et al*[3] provide support for PhaSeal™ in maintaining microbial sterility for 7 days. McMichael *et al*[2] applied the system to vials containing sterile culture media, and entered and retrieved samples from the vial multiple times to simulate use. Samples were removed from the vial at 24, 48, 72, 96, and 168 hours and incubated to investigate microbial contamination. The results showed a contamination rate of 1.8% in 1328 samples by 168 hours. Carey *et al*[3] expanded on the McMichael study and investigated the sterility of culture media vials added to IV bags and found a contamination rate of 0.3% in 331 samples at 168 hours. Samples in both studies which showed initial contamination failed to show further contamination when additional samples were taken at later time points, which may indicate contamination from an external factor, instead of failure of the system itself. A real-world study done by Ho *et al*[4] investigated PhaSeal™ sterility using fluorouracil as the test medium in order to simulate conditions closer to actual practice. Aliquots of fluorouracil were stored using the CSTD and transferred to culture medium in IV bags over 2 weeks. The IV bags did not exhibit any microbial contamination upon visual inspection after incubation and monitoring for 2 weeks, supporting the use of CSTDs in maintaining sterility of the product. Limitations regarding the use of CSTDs include industry sponsorship of the studies through unrestricted research grants (with the possible exception of the Ho study; funding source not specified) and the limited amount of published literature currently available. It should be noted that at the time of the literature review for this proposed mitigation strategy, there was no fully published evidence available in support of other CSTD vendors apart from what is mentioned above. In conclusion, the available published literature provides evidence supporting the feasibility of using a CSTD to extend the BUD of single-dose vials for up to 7 days.

Recommendations

For commercially available single-dose vials, the NAPRA Model Standards state that if the vial is opened and maintained in a C-PEC that maintains ISO Class 5 air quality, the BUD of the single-dose vial is 6 hours. If the single-dose vial is opened in an environment with air quality worse than ISO Class 5, the recommended BUD is 1 hour. Notwithstanding the implementation of appropriate mitigation strategies, this may lead to significant drug wastage and considerable financial cost. The NAPRA Model Standards do not make any specific statements in

regards to the use of CSTDs in extending the BUD of single-dose vials and therefore this mitigation strategy may not necessarily be the only appropriate method for extending the BUD.

While there is some literature to support the use of the PhaSeal™ system to extend the BUD of single-dose vials, it is not the only CSTD which may be effective and appropriate for this strategy. The National Institute for Occupational Safety and Health defines CSTDs as "a drug transfer device that mechanically prohibits the transfer of environmental contaminants into the system and the escape of hazardous drug or vapor concentrations outside the system."[5]

1.0 Use of CSTDs to extend BUD of single-dose vials	
1.1	A CSTD may be used to reduce the risk of microbial contamination with single-dose vials and to extend the BUD of the single-dose vial from 6 hours, but not exceeding 7 days. In determining whether this strategy is appropriate, consider the following: • The specific device should demonstrate the ability to maintain sterility beyond 6 hours based on reputable published literature and facility-level testing to support the specified storage conditions. • The extended BUD of the single-dose vials (using nutrient or culture media as outlined in the NAPRA Model Standards) should be supported by the results of facility-level sterility testing using the specific device and done in accordance with the NAPRA Model Standards. o A testing frequency of a minimum of once per year is suggested provided ongoing sterility is demonstrated. Repeat testing ensures that the people, processes and devices used to demonstrate initial sterility and to potentially extend the BUD of single-dose vials are continually being evaluated. • Pharmacy personnel involved in the compounding of sterile preparations should pass both an initial and ongoing annual assessment of their competency according to the NAPRA Model Standards, including appropriate use of/training for a CSTD. • The facilities and equipment used for the compounding of sterile preparations should be designed and maintained in accordance with the NAPRA Model Standards.

Dose Rounding

Summary of Key Published Evidence

In a large cohort (n=662) of breast cancer patients receiving FEC chemotherapy with curative intent[6], the clinical impact of a dose-rounding algorithm used to deliver drug doses within 5% of the standard dose derived from body surface area (BSA) was assessed. Patients who received doses higher than calculated from BSA were no more likely to experience acute hematological or non-hematological toxicity than those receiving exact or lower doses.

Lindsey *et al*[7] conducted a retrospective, single centre study examining the potential cost savings by rounding monoclonal antibodies to the nearest vial size. During the one-year study period, rituximab and bevacizumab comprised the majority of doses (> 90%) prescribed and eligible for dose rounding up or down to the nearest vial size. The median percentage rounded was 6.7% and 5.9% for bevacizumab and rituximab, respectively. By implementing a dose rounding policy, a cost savings of 72K USD was achieved.

Winger *et al*[8] assessed the potential cost savings related to a dose-rounding process to a value within 10% of the ordered dose for biologic anticancer agents. Over a 3-month period, dose rounding to a value within 10% was

found to have the potential to reduce drug wastage for 42% of the orders. However, nonadherence for one of the drugs limited the actual cost savings to nearly 16K USD.

A prospective study at the Roswell Park Cancer Institute[9] assessed the cost savings and clinical endpoints associated with a dose rounding strategy of ipilimumab to the nearest available 50 mg vial size. Despite the small sample size, the dose variation from the calculated dose to the rounded dose was 10%. Over the one-year study period, the potential cost savings by rounding ipilimumab to the nearest 50 mg vial was 155K USD although the incremental cost of rounding up on the health care system was not assessed.

Vandyke *et al*[10] conducted a one-year retrospective analysis looking at the financial impact of a pharmacist-managed automatic dose rounding policy for anticancer treatments. This is stratified by biologic anticancer agents (±10%) and cytotoxic anticancer agents (±5%) rounded to the nearest vial size. Close to 200K USD in product acquisition cost was avoided with this policy. Biologic anticancer agents accounted for 7% of the total doses yet 78% of the cost avoidance. Approximately 37% and 4% of the biologic and cytotoxic doses, respectively, were rounded up to the nearest vial size.

Over a 24-month period, Patel *et al*[11] conducted a single institution study to assess the feasibility of dose-rounding rituximab to the nearest available vial size. Of the more than 2000 orders included in this analysis, almost all rituximab doses fell within a 10% dose deviation (comparing prescribed dose to the rounded dose) if rounded to the nearest 100-mg vial size. Two-thirds fell within a 5% dose deviation which aligned with the surveyed oncologists' comfort level. The projected cost savings of this strategy through rounding down were negated by capturing additional costs through rounding up.

Recommendations

The development and introduction of novel oncology drugs into clinical practice has contributed to escalating health care costs and the need for cost-containment strategies as part of a value-for-money framework. Dose rounding may be a viable strategy to minimize drug wastage but also to ensure accuracy and standardization during drug preparation. Most dose rounding protocols address traditional chemotherapy and support rounding to within 5% to 10% of the ordered dose. This practice is based on variances within dose calculations, pharmacokinetic principles, clinical evidence, and both inter- and intra-patient variability in drug clearance.[7] Although evolving, the current clinical evidence supporting dose rounding of monoclonal antibodies (i.e. biologic anticancer agents) is less robust, and extrapolating guidance from traditional chemotherapy may be problematic due to differences in dosing strategies as well as pharmacokinetics and pharmacodynamics.

The Hematology/Oncology Pharmacy Association in the United States published a position statement entitled "Dose Rounding of Biologic and Cytotoxic Anticancer Agents."[12] This document is intended to serve as guidance for facilities/organizations as local dose-rounding policies are developed, and is supported by members of this Working Group. It has also been reviewed and endorsed by the International Society of Oncology Pharmacy Practitioners and the National Comprehensive Cancer Network.

A strategy of dose rounding, whereby the calculated weight-based or BSA-derived systemic therapy dose is adjusted by a set variance limited by vial size availability, may be used as a means of minimizing drug wastage with single dose vials, in parallel with other mitigation strategies. Please note that drug wastage is not reimbursed by PDRP or any other Cancer Care Ontario program.

2.0 Dose Rounding	
2.1	A dose rounding strategy to within 10% of the calculated dose, to the nearest available vial size, may be considered as a mitigation strategy. This informed clinician decision should be guided by patient-specific and disease-related factors, goal(s) of treatment, and expected toxicities. • The recommendations outlined above apply to both traditional cytotoxic anticancer treatments as well as monoclonal antibodies and other biologic agents (including antibody-drug conjugates) used for anticancer treatment. • A dose rounding threshold to within 10% of the calculated dose to the nearest available vial size was the most commonly cited clinical guidance provided by respondents to Cancer Care Ontario's survey of Ontario Cancer Leads and their Drug Advisory Committees.
2.2	The same threshold for dose rounding may be utilized for adjuvant/curative and palliative-based therapies taking into account clinical effectiveness and patient safety with the overall goal of optimizing patient outcomes.
2.3	Institutions should develop local policies around site-specific dose rounding practices (including exceptions to the policy) and to ensure clear and concise documentation of such practices.

Facility Level Sterility Testing

Summary of Key Published Evidence

Key supporting references, such as the United States Pharmacopeia (USP) and the National Formulary (NF) (USP-NF) General Chapter <797> "Pharmaceutical Compounding-Sterile Preparations" and General Chapter <71> "Sterility Tests", do not address the frequency of testing for extending the BUD of single-dose vials required to adhere to the NAPRA Model Standards.

USP-NF General Chapter <797> requires that all personnel compounding sterile preparations are adequately educated, instructed and skilled to perform proper aseptic technique[13]. The knowledge base and the skills of each compounder should be evaluated when hired (regardless of previous experience) and at least annually thereafter. A media-fill or process-simulation test mimics an actual and entire compounding procedure, using a suitable growth medium (e.g. tryptic soy broth) in place of the typical ingredients, to prepare a CSP from start to finish. The number of media-fill tests and frequency of testing are less well defined in the current literature. The only stipulation is that testing must occur at least annually for low- and medium-risk compounding, and at least twice yearly for high-risk compounding.

Recommendations

The NAPRA Model Standards currently assign a BUD of 6 hours for opened single dose vials when maintained in an ISO class 5 environment within a C-PEC. The BUD is reduced to 1 hour if the vial is opened in an environment with worse air quality than ISO class 5. Any site attempting to extend the BUD of single-dose vials must comply with ongoing facility-level sterility testing to ensure protection from microbial contamination under the required storage conditions.

3.0 Facility Level Sterility Testing	
3.1	Facility level sterility testing may be used to support extending the BUD of single-dose vials provided the ISO air quality of the particular storage condition(s) meets the appropriate class.

3.2	Where the BUD of single-dose vials are extended to more than 6 hours, sites must have regard to sections 3.2a, 3.2b, 3.2c, and 3.2d.
a	Facility-level sterility testing must include key elements of the NAPRA Model Standards' Quality Assurance Program: • The Quality Assurance Program must have 4 components: verification of equipment (including the C-PEC), verification of controlled areas (clean room and anteroom), verification of aseptic compounding processes, and verification of final preparations. In addition: o Certification of controlled rooms and C-PECs must be done at least every 6 months. o Environmental verification (sampling of air quality) must be conducted every 6 months. o Compounding personnel must pass an initial and ongoing annual assessment of their competency in sterile compounding according to NAPRA Model Standards. • Each of the 4 components and its activities must be documented and be easily retrievable.
b	For sites not adopting use of a CSTD, a formal testing protocol should be established and validated at the local level to ensure ongoing sterility of extending the BUD of single-dose vials beyond 6 hours.
c	The extended BUD of the single-dose vials should be supported by the results of the sterility testing that was initially performed to validate the sterility testing process under the specified storage conditions, taking into account environmental factors such as the container, temperature and light exposure. • Sterility testing must consistently be negative for microbial contamination. • BUD of the single-dose vials should not be extended if the results from the most recent facility testing process did not pass the sterility standards.
d	The facilities and equipment for the compounding of hazardous and non-hazardous sterile preparations must be designed and maintained in accordance with the NAPRA Model Standards.
3.3	Facility level sterility testing should be a collaborative process between the Departments of Pharmacy and Microbiology based on local/institutional Standard Operating Procedures. Some or all of these services may also be outsourced to a USP-adherent commercial laboratory provider.

Automated Robotic Dispensing Unit (ARDU)

Summary of Key Published Evidence

To date, no published evidence is available to directly support the use of ARDUs to extend the BUD of the single-dose vials in accordance with the NAPRA Model Standards.

ARDUs have a significant upfront investment and ongoing maintenance costs. However, simulation modeling provides some evidence to support that the ability of ARDUs to prevent medication errors which may result in cost avoidance through direct medical costs[14].

Recommendations

4.0 Use of an Automated Robotic Dispensing Unit	
4.1	ARDUs can be used as biological safety cabinets to maintain the sterility of single-dose vials while providing additional storage capacity when stored at room temperature and, potentially, under refrigeration.
4.3	ARDUs may be able to support extending the BUD of single-dose vials with a potential add-on of expanded storage capacity for room temperature and/or refrigerated items. A formal testing protocol should be established and validated at a local level in support of this.

Other Strategies

Summary of Key Published Evidence

Dose Banding

Dose banding is defined as a system whereby drug doses calculated by any method are grouped and rounded to a set of predefined standard doses.

Chatelut *et al*[15] conducted a study comparing dose banding with individualized BSA dosing and fixed dosing according to pharmacokinetic criteria for six commonly utilized chemotherapeutic drugs. Their conclusion was that dose banding in place of individualized dosing resulted in no significant difference in inter-individual plasma exposure.

Other authors have suggested that a system of dose banding may reduce patient wait times, drug wastage and medication errors while also improving pharmacy efficiency in the preparation of CSPs[16, 17].

Recommendations

5.0 Other Strategies	
5.1	Dose banding may be considered for select drugs to help with system efficiencies, reduce wait times and minimize drug wastage. • The BUD of the CSP produced as a result of the dose banding strategy should be supported by chemical and physical stability data and adhere to the BUD recommendations outlined in the NAPRA Model Standards.
5.2	Where permissible, a strategy whereby patient treatment schedules are coordinated (i.e., "batching") and/or restricted to certain days of the week (i.e., for vial sharing purposes) may be considered based on local practices.

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