

## Dose Rounding of Biologic and Cytotoxic Anticancer Agents

*A Position Statement of the Hematology/Oncology Pharmacy Association*



**HOPA**  
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## Reviewed and Endorsed by

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## Background and Executive Summary

The cost of cancer care in the United States is expected to exceed \$170 billion in 2020 and represents one of the fastest-growing costs in health care.<sup>1</sup> Rounding of drug doses to the nearest vial size when the difference is less than an established percentage is an important initiative that can be implemented to minimize drug waste, ensure accuracy during drug preparation, and reduce healthcare expenditures. Dose rounding is especially relevant for drugs that are supplied in single-use vials in a preservative-free formulation. Various institutions have implemented dose-rounding policies, which generally allow dose rounding within 5%–10% of the ordered dose for biologic and cytotoxic anticancer treatments.<sup>2-4</sup> Some institution-specific policies permit more liberal rounding in some circumstances: with monoclonal antibodies versus cytotoxic chemotherapy or for palliative therapy versus treatment with curative intent. Although the impact of dose rounding on disease progression and overall survival is expected to be non-influential, few studies have evaluated this question. Single-institution cost analyses estimate savings ranging from tens of thousands to millions of dollars, depending on the drug and the number of doses dispensed per patient per year.<sup>2-9</sup>

This document is intended to serve as a guideline for use during the development of a dose-rounding policy and to support and validate already existing policies. Although other strategies—such as using closed-system transfer devices, billing for waste, using syringe-increment rounding, and rounding doses to a certain decimal place—can be used to reduce costs, these should be discussed separately and are not treated in this position statement.

Some centers may avoid dose rounding for pediatric patients or patients under a designated weight because of the futility of dose rounding for amounts consistently much smaller than the amount a vial contains.<sup>9</sup> Although this position statement does not include data from the pediatric population, clinicians could reasonably use the recommendations herein for larger pediatric patients or adult patients being treated on pediatric protocols based on their clinical judgment.

### Dose Rounding for Monoclonal Antibodies

**Recommendation 1:** On the basis of the published data, HOPA recommends that monoclonal antibodies and other biologic agents currently available be dose rounded to the nearest vial size within 10% of the prescribed dose.

**Recommendation 2:** For monoclonal antibodies with a cytotoxic constituent, HOPA recommends using the dose rounding applied to cytotoxic agents.

Monoclonal antibodies and other biologic therapies (e.g., interleukin and interferon) have a targeted therapeutic effect on tumor cells.<sup>10</sup> The pharmacologic mechanism of action varies and may include disruption of a biologic messaging process (e.g., with cetuximab), cellular cytotoxicity (e.g., with rituximab), or delivery of a toxic conjugate (e.g., with brentuximab vedotin). Because of the complex processes required to manufacture them, monoclonal antibodies are expensive to produce.<sup>11</sup> Monoclonal antibodies are administered intravenously,

and most are packaged in single-use, preservative-free vials, so they are used just once and have short beyond-use dating.<sup>5</sup>

Dose rounding of multiple monoclonal antibodies (including rituximab, bevacizumab, trastuzumab, cetuximab, ipilimumab, and gemtuzumab) has been reported in the literature.<sup>2,3</sup> Current literature focuses on the impact of dose rounding on lowering costs and reducing medication waste; however, studies have not addressed the effects of dose rounding on efficacy.<sup>3</sup> Dose-rounding options reported in the literature include rounding to the nearest vial size if the rounded dose falls within 10% of the prescribed dose,<sup>2</sup> rounding down to the nearest vial size if the dose falls within 5% or 10% of the prescribed dose,<sup>3</sup> and rounding to the nearest vial-size increment (e.g., 50-mg vial for ipilimumab).<sup>5</sup> In one example, projected annual savings for rounding bevacizumab, trastuzumab, and cetuximab down to the nearest vial size within 5% and 10% of the prescribed dose were \$181,944 and \$337,755, respectively.<sup>3</sup> Winger and colleagues showed a cost savings of \$124,434 over a 3-month period for seven biologic anticancer agents when biologic agents within 10% of the prescribed dose were rounded to the nearest vial size.<sup>4</sup>

Monoclonal antibodies have been tested using a wide range of doses, with some drugs not reaching a maximum tolerated dose (MTD). Nivolumab has been evaluated in doses ranging from 0.1 to 10 mg/kg, and an MTD was not reached within this dosing range.<sup>12</sup> Weber and colleagues reported giving multiple doses up to 10 mg/kg and single dosing up to 20 mg/kg of ipilimumab without reaching an MTD.<sup>13</sup> For ipilimumab, U.S. Food and Drug Administration (FDA)-approved dosing ranges from 3 mg/kg to 10 mg/kg based on indication.<sup>14</sup> These examples illustrate the wide therapeutic dosing range of monoclonal antibodies. Moreover, pharmacokinetic studies have demonstrated significant interpatient variability in drug exposure. As **Table 1** demonstrates, the coefficients of variation (CV) for the measurements of area under the curve (AUC) for biologic drugs can vary significantly. The wide therapeutic dosing range and CV for AUCs for the monoclonal antibodies support liberal rounding without raising safety concerns.

**Table 1. Coefficients of Variation for the Measurements of Area Under the Curve for Biologic Anticancer Drugs<sup>9</sup>**

Drug	%
ado-trastuzumab	11–34
bevacizumab	15–53
brentuximab vedotin	25–30
Cetuximab	22–65
Ipilimumab	25–36
Rituximab	45
Trastuzumab	25–35
ziv-aflibercept	15–37

For antibody-drug conjugates (ADCs), which are defined as monoclonal antibodies linked to a cytotoxic constituent (such as ado-trastuzumab emtansine), rounding recommendations can follow those of either monoclonal antibodies or cytotoxics. The reason for categorizing ADCs as biologics is that the targeted delivery of the cytotoxic constituent is conferred by its conjugation to a monoclonal antibody. By contrast, support for categorizing ADCs as cytotoxics is based on the toxic potential of the cytotoxic constituent. Some institutions round ADCs on the basis of the monoclonal antibody carrier, and others round ADCs on the basis of the cytotoxic component. Arguments can be made for both, but HOPA prefers the conservative approach of rounding ADCs according to the cytotoxic rounding recommendations (if institutional policies for dose rounding use different percentages for monoclonal vs. cytotoxic agents) because of the narrower therapeutic range of these drugs.

## Dose Rounding for Cytotoxic Chemotherapy

**Recommendation 3:** On the basis of the available literature, HOPA recommends that traditional cytotoxic agents be considered independently for dose rounding within 10% of the prescribed dose.

The rationale for rounding to an amount within 5%–10% of a prescribed dose is based on the premise that this practice will not have a negative impact on the safety or effectiveness of the therapy. Although dose rounding for traditional cytotoxic chemotherapy has been the subject of fewer published studies than dose rounding in other areas, the potential impact and feasibility of a 5% rounding allowance for cytotoxic drugs has been evaluated and published in multiple reports.<sup>6, 9</sup> Cytotoxic chemotherapeutic agents are traditionally considered to have a narrow therapeutic index. Doses approved for treating malignancies are usually based on MTDs defined in clinical trials. MTDs are determined in phase 1 studies using dose-escalation methods, often increasing doses by 25% or more. When an MTD is reached, the dose level below the defined toxic level is recommended for further investigation in larger phase 2 studies.<sup>15</sup> A dose-escalation strategy for liposomal doxorubicin involved seven dose levels, including three liposomal doxorubicin dose increases from  $20 \text{ mg/m}^2$  to  $30 \text{ mg/m}^2$  (a 50% increase), from  $30 \text{ mg/m}^2$  to  $40 \text{ mg/m}^2$  (a 33% increase), and from  $40 \text{ mg/m}^2$  to  $50 \text{ mg/m}^2$  (a 25 % increase).<sup>16</sup> Another illustration is pemetrexed  $600 \text{ mg/m}^2$ , which was chosen as a safe dose in phase 1 trials, but because of bone marrow suppression and gastrointestinal toxicity, the dose was empirically reduced to  $500 \text{ mg/m}^2$ . This reduction occurred prior to the discovery that vitamin supplementation reduces these toxicities. Therefore, with appropriate ancillary medication therapy, it is reasonable to believe that a dose in the range of  $450\text{--}550 \text{ mg/m}^2$  can be given safely and effectively and avoid drug waste.<sup>17</sup> Furthermore, standard dose adjustments to improve patient tolerance and response are generally in the range of 20%–30%, which exceeds the amounts for reported dose rounding several fold. The lymphoma regimen dose-adjusted EPOCH includes a defined dose escalation and reduction schema using increments of 20%, which is based on hematologic toxicity documented with the preceding cycle of therapy. The initial trial evaluating this regimen reported that dose escalation occurred with 58% of treatment cycles without producing unacceptable toxicity.<sup>18</sup>

Rounding cytotoxic agents by 10% is rational in the context of the amount of dose adjustments made for patient tolerance and tumor response ( $\geq 20\%$ ). The National Cancer Institute Guidelines for Auditing Clinical Trials defines a major deficiency—a variance from protocol-specified procedures that makes the resulting data questionable—as dose deviations, modifications, or incorrect calculations if the error is greater than 10% over or 10% below the intended dose.<sup>19</sup> Moreover, dose rounding in amounts of 10% for both cytotoxic and biologic products streamlines the process for staff.

An additional consideration is that despite the use of surface area- and weight-based dosing for most anticancer treatments, the effect on the AUC of dose rounding within 10% will generally be eclipsed by the degree of interpatient pharmacokinetic variability that ultimately determines systemic drug exposure.<sup>9</sup> One study reported that systemic concentrations of only 5 of 33 investigational anticancer drugs (docosahexaenoic acid–paclitaxel, fluorouracil/eniluracil, paclitaxel, temozolomide, and troxacicabine) administered to 1,650 patients were normalized

with the surface area–based dose calculation. The CV for drug clearance ranged from 13% to 151% and from 22% to 170% for orally and intravenously administered drugs, respectively.<sup>20</sup>

### Potential Differences in Dose-Rounding Limits Depending on the Intent of Treatment

**Recommendation 4:** On the basis of the inference that dose rounding will not influence clinical safety or effectiveness, HOPA supports use of the same threshold for dose rounding of anticancer drugs used for palliative and curative therapy.

Some providers support dose rounding within 10% for palliative therapy and within 5% for curative therapy. They base their support on the view that the desired balance between patient safety and effectiveness may differ, depending on whether the therapy is intended to be palliative or curative.<sup>2,3,8</sup> Standard dose adjustments to improve patient tolerance and response are generally in the range of 20%–30%, which is several-fold the amounts reported for dose rounding.<sup>8,14,15,18</sup>

### Recommendations on Dose Rounding for Oral Chemotherapy

**Recommendation 5:** When oral chemotherapy is supplied in more than one strength of capsule or tablet, it is advantageous to use one strength and to round the final dose to avoid confusion for the patient and to eliminate the possibility of multiple copayments.

The topic of dose rounding for oral oncolytics has not been well covered in the literature and is limited to the tablet or capsule size of the drug. The majority of oral oncolytics have flat-based dosing, though some are dosed on the basis of body surface area and weight. Oral oncolytics should not be crushed or cut; they should be swallowed whole. Prescribing multiple strengths of an oral medication increases the opportunity for medication errors.<sup>21</sup> According to the American Society of Clinical Oncology/Oncology Nursing Society Chemotherapy Administration Safety Standards, doses may be rounded to the nearest capsule or tablet size.<sup>22</sup>

### Implementation of an Institutional Dose-Rounding Policy

**Recommendation 6:** Institutions should develop policies through interdisciplinary efforts, which can be endorsed by a policy-managing body such as a pharmacy and therapeutics (P&T) committee or an oncology subcommittee. The policy should specify the cytotoxic and monoclonal antibody classes that are subject to dose rounding and the rounding limits for each class; describe the process for rounding ordered doses and documenting such changes; and spell out any applicable exceptions, such as drugs supplied in multidose vials or in circumstances where prescribers should be consulted prior to rounding by the pharmacist.

Below is an example of wording that may be added to a current chemotherapy policy:

**Chemotherapy dose rounding:** Ordered chemotherapy doses may be rounded up or down by \_\_\_\_% by the pharmacist during the verification process without prior authorization of the ordering

physician. This may be done to avoid drug waste and is approved by the \_\_\_\_ policy, which was approved by the \_\_\_\_ committee on \_\_\_\_.

For orders where dose rounding has been applied, reference to the ordered dose and the rounded dose should be readily available (i.e., in documentation on the medication administration record and/or prescription label or within the medical record). An example of the wording in this documentation: Dose changed from \_\_ mg to \_\_ mg per dose-rounding policy. Change within \_\_ % (dosed at \_\_mg/\_\_ ) by \_\_\_\_\_ (name of pharmacist) on \_\_\_\_ (date of change). These references serve to document the application of rounding practices and provide opportunities for other healthcare providers to independently validate the rounding and assess its appropriateness for the patient. When possible, dose rounding should be automated by the electronic health record in accordance with institutional policy. Automated rounding removes the need for manual entry of the rounded dose, which presents an opportunity for human error.

Although nonmalignant uses of these agents are outside the scope of this position statement, institutions could also consider applying dose-rounding practices to such uses.

### Exceptions and Special Considerations

Each institution should establish exceptions to its dose-rounding policy. Such exceptions include drugs that patients receive in the clinical-trial setting, because dose rounding could be considered a breach of protocol.<sup>9</sup> Dose rounding for pharmacokinetically determined doses of anticancer treatments, such as parenteral busulfan, may not be appropriate, especially when rigorous data are needed for institutional data tracking or research analysis.<sup>9</sup>

Patients with major organ dysfunction, poor performance status, an extensive treatment history, relevant enzyme deficiencies, or genetic polymorphisms may not be good candidates for dose rounding upward because small adjustments in the dose could result in significant pharmacokinetic or pharmacodynamic changes that subsequently increase the risk for serious adverse events.<sup>23,24</sup>

Consideration should be given to patients who have had dose reductions because of toxicity when they have demonstrated intolerance to the usual regimen-based dosage(s). Institutions may want to consider only rounding down for this patient population.

Individual institutions will need to assess dose rounding of monoclonal antibodies to the nearest vial size when rounding results in a >10% difference from the ordered dosage.

### Summary

HOPA recommends that each institution develop its own dose-rounding policy that addresses both monoclonal antibodies and cytotoxic drugs. Institutions may consider rounding both monoclonal antibodies or biologic agents and cytotoxic drugs by the same percentage for consistency.

Institutional guidelines for dose rounding of anticancer agents should be based on a collaborative interdisciplinary consensus. Each institution should also establish its own criteria for automatic dose rounding, the allowable percentage, and the processes for operationalizing and documenting any modifications to the original prescribed dose. Exceptions to the dose-rounding policy should be determined a priori. Dose rounding represents a relatively simple cost-saving measure that institutions can implement to reduce waste and healthcare costs.

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