Comparison of Generic Drug Reviews for Marketing Authorization between Japan and Canada

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Abstract
Purpose Generic drugs are assuming an increasingly important role in sustaining modern healthcare systems, as the cost of healthcare, including drug usage, is gradually expanding around the world. To date, published articles comparing generic drug reviews between different countries are scarce.

Objective The objective of this study was to examine generic drug reviews in Japan and Canada.

Methods We surveyed generic drug reviews from Japan and Canada and compared the following points: general matter (application types, type of partial change or Supplement to an Abbreviated New Drug Submission, application and approval numbers, review period, application format, review report, responsibility for review), bioequivalence studies for solid oral dosage forms, and bioequivalence guidelines, guidance, or basic principles regarding various dosage forms.

Results This survey described the many similarities and differences in generic drug reviews between the two countries and points that should be improved to promote better generic drug reviews. In particular, regulations for the definition of the same or different active pharmaceutical ingredients (APIs) are similar for both authorities.

Conclusions The results clarified the future challenges of generic drug reviews, and the differences highlighted by this survey will be important considerations for the future. This is the first article to present and discuss the details of generic drug reviews between Japan and Canada.

Key Points
This article compares and provides a comprehensive discussion of generic drug regulations in Japan and Canada.

The results clarify the future challenges of generic drug reviews, and the differences highlighted by this survey will be important considerations for the future.

1 Introduction

Generic drugs are drug products that have the same active pharmaceutical ingredient (API), dosage form, administration route, intended use, and quality, safety, and efficacy as their innovator or reference drug. Generic drugs play an increasingly important role in sustaining modern healthcare systems, as the cost of healthcare, including drug usage, is gradually escalating around the world. For example, in 2015 in Japan, medical costs were approximately 41 trillion Japanese yen (¥) [1], and prescription drug costs were approximately ¥7.9 trillion, an increase of 9.4% from 2014. Total healthcare expenditure in Canada was 214.9 billion Canadian dollars ($Can) in 2014, and drug expenditure was $Can 33.9 billion, an increase of 0.8% from 2013 [2]. The elderly population (aged ≥65 years) is predicted to increase dramatically in Japan; the United Nations...
estimates the elderly will account for 29.4% of the population in 2025 and 36.3% in 2050 and that the elderly Canadian population will continue to increase to 20.9% in 2025 and 26.4% in 2050 [3]. Japan and Canada expect to increase generic drug usage to reduce healthcare costs, and the Japanese Ministry of Health, Labour and Welfare (MHLW) should promote the use of generic drugs. The Japanese generic drug share is expanding and was 56.2% by volume in September 2015 [4]. According to a Japanese Cabinet decision in June 2015, the MHLW aims to reach a generic drug market share of ≥70% by mid-2017 and ≥80% as early as possible between fiscal year (FY) 2018 and FY 2020 [5, 6]. On the other hand, the Canadian generic drug share was 68.6% by volume in 2015 [7]. (We do not intend to compare the values associated with the generic drug share between the two countries as numeration is not shown).

Generic drugs are reviewed by the Office of Generic Drugs, part of the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan and the Bureau of Pharmaceutical Sciences in the Therapeutic Products Directorate of Health Canada (HC) in Canada. During drug development by the innovator, pharmaceutical companies must evaluate the efficacy and safety of the new drug to evaluate whether the new drug product, including the drug substance, will have a sufficient effect and provide benefit for patients. Obviously, substantial costs are associated with drug development, including conduct of clinical studies, non-clinical studies, quality assurance, and so on. On the other hand, the safety and efficacy of the drug substances (i.e., API) have already been established for generic drugs. Companies creating generic drugs can use excipients and manufacturing methods that differ from those used to manufacture the innovator drugs, and authorities must evaluate the impact of the differences between the generic and innovator drugs, mainly drug products only. Therefore, generic drug applications are mainly evaluated on the basis of the documents to support product quality and bioequivalence submitted by the manufacturer. Bioequivalence studies are commonly used to demonstrate therapeutic equivalence and to compare bioavailability between generic and innovator drugs. Bioavailability is defined as the degree to which a drug is available to a target tissue after administration, which, for oral drugs, reflects the rate and extent of gastrointestinal tract absorption. In particular, in generic drug development, applicants must evaluate the relative rate and extent of absorption of an API or a metabolite released from a drug product between two products. If the 90% confidence interval (CI) of the relative ratio of the test (generic) to the reference (innovator) drug for the area under the curve (AUC) and peak plasma concentration ($C_{max}$) (only the geometric mean ratio [GMR] for $C_{max}$ is used in Canada) satisfy the specified bioequivalence criteria, generic drugs are expected to be therapeutically equivalent and to possess the same safety and efficacy as their corresponding innovator drugs.

However, no comparisons of generic drug regulations between other countries have been published. The objective of this study was to examine generic drug reviews in Japan and Canada. We compared generic drug reviews for the two countries, focusing on application type, numbers of applications and approvals, review period, application format, review report, acceptance criteria for bioequivalence studies of solid oral dosage forms, and published bioequivalence guidelines, guidances, and basic principles. The results highlighted the similarities and differences between generic drug reviews and clarified future challenges of such reviews in the two countries.

2 Methods

In February 2017, we surveyed public documents and guidelines pertaining to generic reviews, and each reviewer collected information relating to generic drug procedures. In particular, we mainly investigated the information available on the website of the regulatory body (i.e., Japanese MHLW, National Institute of Health Sciences [NIHS], and HC) as well as published articles and compared the generic drug reviews according to the following headings and reference information:

1. General matters: definition of generic drugs, application types, type of partial change or Supplement to an Abbreviated New Drug Submission (SANDS), number of applications and approvals, review period, application format, and review report [8–15].
2. Bioequivalence studies for solid oral dosage forms [16–21].
3. Bioequivalence guidelines, guidances, or basic principles regarding various dosage forms [16–20, 22–33].

3 Results

Table 1 summarizes the results of the comparisons of the definition of generic drugs, requirements for development of strengths, application types, type of partial change or SANDS, number of applications and approvals, review period, application format, review report, and agency responsible for the review.

3.1 Definition of Generic Drugs

Generic drugs are drug products that have the same API, dosage form, administration route, intended use, and quality, safety, and efficacy as innovator drugs. The PMDA
generally considers different hydrate or crystalline forms to those found in the innovator drug as being the same API if such differences do not influence the safety and efficacy of the product. However, if the salts, esters, ethers, isomers, mixtures of isomers, complexes, or derivatives of an active substance differ from those in the innovator drug, the PMDA requires an application for a new drug rather than for a generic drug. HC, on the other hand, considers the use of anhydrous, anhydrate, and various hydrated, unsolvated, and various solvated forms of the same active moiety to be suitable for generic applications, whereas different complexes, esters, or salts and different isomers or mixtures thereof are considered new drugs [8, 9].

### 3.2 Requirements for Development of Strengths

Generic product applicants in Japan must develop the same strengths that have been marketed for the innovator products, as specified in the domestic notification. Similarly, HC also recommends this, but it is not mandatory.

### 3.3 Application Types

In Japan, applications are divided into either new generic drug applications (the first application for marketing authorization) or partial change approval applications (for a major change; submitted post-approval). In addition, a minor change application can also be submitted, for which the PMDA does not conduct a review at the time of submission; instead these minor change contents are reviewed at the time of the next partial change application, which also includes an assessment of whether the minor changes are appropriate. The PMDA specifies whether the contents are a partial change or a minor change as presented within the manufacturing method section of the approval application form, using the following description [10].

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**Table 1** Comparison of generic drug reviews for marketing authorization between Japan and Canada

| Japan                                                                 | Canada                                                                 |
|----------------------------------------------------------------------|------------------------------------------------------------------------|
| **Definition of the same API**                                       | Different hydrate or crystalline forms                                  |
|                                                                      | Different anhydrous, anhydrate, various hydrated, unsolvated, and various solvated forms |
| **Definition of a different API**                                     | Different salts, esters, ethers, isomers, mixtures of isomers, complexes, or derivatives |
|                                                                      | Different complexes, esters, salts, isomers or mixtures                |
| **Requirements for development of strengths that have been marketed for the innovator products** | It is mandatory to develop all strengths                                  |
|                                                                      | Not mandatory but to be recommended                                    |
| **Application types**                                                 | New generic drug application; partial change approval application       |
|                                                                      | ANDS; SANDS; NC                                                         |
| **Type of partial change or SANDS**                                   | Indication and effects; dosage and administration; specifications and test methods; storage method and validity period; manufacturing method; formulation; manufacturing site |
|                                                                      | Indication and effects; dosage and administration; specifications and test methods; storage method and validity period; manufacturing method; formulation; manufacturing site; addition of a dosage form or strength |
| **Application number**                                                | New: 701<sup>a</sup>                                                   |
|                                                                      | Partial: 2313<sup>a</sup>                                               |
| **Approval number**                                                   | New: 775<sup>a</sup>                                                   |
|                                                                      | Partial: 1882<sup>a</sup>                                               |
| **Review period**                                                     | New: 12 months                                                         |
|                                                                      | Partial: 3, 6, or 12 months                                             |
|                                                                      | ANDS: 180 or 300 days                                                  |
|                                                                      | SANDS: 60, 180, or 300 days                                            |
|                                                                      | NC: 90 or 180 days                                                     |
| **Application format**                                                | Recommend application by CTD/e-CTD                                      |
|                                                                      | e-CTD                                                                  |
| **Review report**                                                     | Pilot stage                                                            |
|                                                                      | Positive case: request                                                 |
|                                                                      | Negative case: all ANDS and SANDS                                      |
| **Responsible for review**                                           | Each reviewer conducts a review of both quality and bioequivalence     |
|                                                                      | Each reviewer conducts a review of either quality or bioequivalence    |

<sup>a</sup> Data from FY 2012; numbers may change slightly by search style

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*ANDS* abbreviated new drug submission, *API* active pharmaceutical ingredient, *CTD* common technical document, *e-CTD* electronic-CTD, *NC* notifiable change, *SANDS* supplement to an abbreviated new drug submission
Target/set values of process parameters and standard conditions

Partial change matters: \{ \}
Minor change matters: \[ \]

Other than target/set values

Partial change matters: All parts without the parentheses
Minor change matters: ‘’ ‘’

The approval application form contains the indication and effects, dosage and administration, specifications and test methods, storage method and validity period, manufacturing method, formulation, and manufacturing site. All items are generally partial change approval matters other than the minor change matters relating to the manufacturing method as outlined above.

In Canada, three application types are possible: abbreviated new drug submission (ANDS), SANDS, and notifiable change (NC) [11]. ANDS is equivalent to the Japanese new generic drug application. The types of SANDS are similar to a partial change approval application in Japan, except for the addition of a dosage form or strength (which, in Japan, would be a new generic drug application), and the management methods also differ [12, 13]. In particular, with regard to quality-related sections, HC requires a highly detailed report (supplement or annual notification) for each change in the contents, based on the common technical document (CTD), module 3 in the guidance [13]. For example, for “Change in the composition of a solution dosage form,” if the level of change is not considered significant according to published guidelines, the change may be filed as an annual notification rather than a SANDS (in Japan, this would generally be a partial change application). A NC refers to change procedures for labelling; two kinds of risk management change are associated with this depending on whether or not the changes affect the conditions of use.

3.5 Application Format, Review Report, and Responsibility for the Review

There is currently no standard format for generic drug applications in Japan; the PMDA recommends the CTD or electronic-CTD (e-CTD) format for applications. In March 2016, the MHLW notified sponsors that they would be expected to use the CTD format for applications after March 2017 [15], whereas HC incorporated the e-CTD format in 2011.

Regarding the review report, the PMDA is the pilot stage, and considers the report to assure transparency of the review for new generic drugs. Conversely, HC makes the review reports available upon request or when a negative decision is rendered (i.e., a Notice of Deficiency, a Notice of Deficiency/Withdraw, a Notice of Noncompliance, or a Notice of Noncompliance/Withdraw) for all submission types, including ANDSs and SANDSs.

In the PMDA, each reviewer conducts a review of both quality and bioequivalence components, whereas each reviewer within HC is responsible for conducting a review of either the quality or the bioequivalence study. Obviously, both authorities decide upon the appropriateness of an evaluation in a team as needed.

3.6 Bioequivalence Studies for Solid Oral Dosage Forms

Bioequivalence studies are typically conducted in healthy volunteers with a randomized, two-period, two-sequence, two-treatment, single-dose crossover design...
study to minimize variability. If the recruitment of healthy volunteers raises safety concerns, recruitment of patients becomes necessary. Japanese guidelines do not clearly specify a number of subjects required (a sufficient number of subjects for assessing bioequivalence should be included) [16], whereas HC guidelines state a minimum number of 12 but a larger number is usually required [17]. In Japan, drug products are taken with 100–200 ml (normally 150 ml) of water, whereas HC advises 150–200 ml.

Generally, bioequivalence studies of oral immediate-release (IR) drug products are conducted with subjects in a fasted state in both Japan and Canada. In Japan, bioequivalence studies for narrow therapeutic index drugs (NTIDs) [18], highly variable drugs (HVDs), and delayed-release (DR) drugs are conducted under the same fundamental conditions as for IR drug products (i.e., in a fasted state) (Table 2). On the other hand, HC recommends evaluating bioequivalence under both fasted and fed states. Both countries use AUC_{\text{t}} (AUC from zero to the final sampling time t) and C_{\text{max}} as the primary endpoints, but the evaluation method for C_{\text{max}} differs. The PMDA requires the 90% CIs for the ratio of test and reference products to be within 80–125% for both AUC_{t} and C_{\text{max}}. If these criteria are not satisfied, the PMDA allows a second standard: GMRs should be within 90–111% for both parameters. These criteria are adopted for the solid oral dosage forms, including NTID, HVD, and modified-release (MR) products. However, if the second standard is used for ER drug products, the criterion for the dissolution test is stricter than for other oral drug products [16, 20].

HC requires the 90% CI for the GMR to be within 80.0–125.0% for the AUC_{t} for general IR and MR (DR and ER) drug products but has a different criterion for C_{\text{max}}: the GMR of the test and reference products must lie within 80.0–125.0%. For CDD products, HC adopts a narrower criterion for the AUC_{t}; the 90% CI for the GMR should lie within 90.0–112.0%, whereas the 90% CI for the GMR for the C_{\text{max}} must be between 80.0–125.0%. In April 2016, HC published a new policy for HVD products [21]; this new concept permits wider acceptance criteria for the AUC_{t} only, based on the within-subject coefficient of variation (CV) (as shown in Table 2). A replicate design is used to determine the within-subject CV, and the reference products are administered at least twice. The GMR must then be within 80.0–125.0%. In addition, this approach does not apply for CDD products.

### 3.7 Bioequivalence Guidelines, Guidances, or Basic Principles Regarding Various Dosage Forms

Figure 1 shows the bioequivalence guidelines, guidances, or basic principles and describes the biowaiver guidelines published in Japan and Canada. Both countries have published bioequivalence guidelines or guidances for oral [16, 17, 19] and dermatological dosage forms [22, 23]. In March 2016, the MHLW published two new basic principles: one relates to bioequivalence evaluation of dry powder inhaler drug products [24, 25] and the other refers to biowaiver of aqueous solutions of ophthalmic dosage forms [26]. For ophthalmic aqueous solutions, Japan generally requires human bioequivalence studies with pharmacodynamic or clinical endpoints. If generic drug applicants can ensure qualitative (Q1) and quantitative (Q2) sameness (i.e., the same excipients in the same amount or concentration) to the innovator products and similar physicochemical properties (e.g., pH, viscosity, osmolarity, and so on), the PMDA consider acceptance of a biowaiver. In addition, the PMDA recommends that a detailed discussion and consultation be had with the agency if the applicants conduct human bioequivalence studies or hope to submit a biowaiver for aqueous solutions of ophthalmic dosage forms. Currently, Japanese guidelines or basic principles permit biowaivers only for intravenous injections administered as aqueous solutions and ophthalmic aqueous solutions.

Conversely, HC has published guidelines as follows:

- short-acting beta_{2}-agonist, metered dose inhalers in April 1999 [27],
- quality of aqueous solutions, including aqueous solutions for inhalation, in February 2005 [28],
- quality of inhalation and nasal products in April 2006 [29],
- inhaled corticosteroid products for the treatment of asthma in September 2011 [30],
- steroid nasal products for the treatment of allergic rhinitis in September 2011 [31].

With regard to orally inhaled drug products, both countries commonly require in vitro, pharmacokinetic, and pharmacodynamic or clinical endpoint studies for evaluation of bioequivalence. Two guidances relate to biowaivers for various types of aqueous solutions (published February 2005 [28]) and to the biopharmaceutics classification system (published May 2014 [32]). HC adopts Q1 sameness and Q2 similarity for aqueous solutions, where Q2 similarity means within ±10% of the amount or concentration of each excipient. Additionally, the comparison results of the physicochemical properties must satisfy the ±10% requirement, and the results of a Q1 and Q2 analysis of the...
4 Discussion

We surveyed generic drug reviews in Japan and Canada with respect to general matters, bioequivalence studies for solid oral dosage forms, and bioequivalence and biowaiver guidelines, guidances, or basic principles regarding various dosage forms. First, we confirmed the definitions and requirements of generic drug development. In Japan, generic drug applicants must develop all strengths approved for the innovator product to provide complete interchangeability, but this is not mandatory in Canada. This represents a significant difference in the regulatory requirements between the two jurisdictions. For example, where there are multiple strengths of marketed innovator orally inhaled drug products, generic drug applicants must scientifically prove bioequivalence for all strengths in Japan. Regarding application types, including the type of partial change or SANDS, both countries adopt a similar system, but the PMDA does not have a specific submission type for labelling changes (i.e., similar to NCs for HC). The

| Table 2 Bioequivalence acceptance criteria for solid oral dosage forms |
|-------------------------|-------------------------|
| IR                      | Japan                   |
|                        | Fasted state            |
|                        | Parameter: AUC<sub>t</sub> and C<sub>max</sub> |
|                        | First: 90% CIs for the GMRs within 80–125% |
|                        | Second: GMRs within 90–111%<sup>a</sup> |
| NTID or CDD             | The same requirements as above |
| HVD                     | The same requirements as above |
| MR                      | DR                      |
|                        | Fasted state            |
|                        | Parameter: AUC<sub>t</sub> and C<sub>max</sub> |
|                        | First: 90% CIs for the GMRs within 80–125% |
|                        | Second: GMRs within 90–111%<sup>a</sup> |
|                        | ER                      |
|                        | Fasted and fed state    |
|                        | Parameter: AUC<sub>t</sub> and C<sub>max</sub> |
|                        | First: 90% CIs for the GMRs within 80–125% |
|                        | Second: GMRs within 90–111%<sup>b</sup> |
|                        | DR and ER               |
|                        | Fasted and fed state    |
|                        | Parameter: AUC<sub>t</sub> and C<sub>max</sub> |
|                        | AUC<sub>t</sub>: 90% CI for the GMR within 80.0–125.0% |
|                        | C<sub>max</sub>: GMR within 80.0–125.0% |

<sup>a</sup> In addition to the GMR requirements, the following standards must be satisfied: (1) the total sample size of the initial bioequivalence study should not be <20 (per group) or the pooled sample size of the initial and add-on subject studies should not be <30; (2) the dissolution rates of generic and innovator drug products should be similar under all conditions tested.

<sup>b</sup> In addition to the GMR requirements, the following standards must be satisfied: (1) the total sample size of the initial bioequivalence study should not be <20 (per group) or the pooled sample size of the initial and add-on subject studies should not be <30; (2) the criterion for the dissolution test is narrower than for IR and DR drug products: the dissolution rates of generic and innovator drug products should be equivalent under all conditions tested.

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number of applications and approvals different substantially (particularly the number of partial change or SANDS applications and approvals). This may be because HC provide guidance specifying the reporting category (supplement or annual notification) for each change in the contents, based on the CTD module 3 [13], whereas Japan does not have such documents. We think many partial change approval applications are related to quality components such as the manufacturing method and/or the manufacturing site addition.

It is important that reviews are swift and effective. Both authorities specify review timelines in published documents. In addition, HC include a screening period prior to review to ensure the proper submission materials are provided during the evaluation period. If HC cannot confirm the suitability of submission materials, the applicants are issued with a screening deficiency notice identifying the deficiencies, and the review does not start. Currently, Japan does not have such a system; instead, a checklist is available to ensure the appropriate application documents are received for review [15]. Japan may also consider applying a similar system with respect to screening using a checklist. Additionally, Japan will need to accelerate the application of e-CTDs to make the review process more efficient.

We then compared the bioequivalence acceptance criteria for solid oral dosage forms. The basic concept is similar; that is, that the 90% CI for the GMR is within 80–125%. A characteristic feature of the PMDA is to adopt a second standard. If the first standard, where the 90% CI for the GMR should lie within 80–125%, is not met, the PMDA states that the GMR can lie within 90–111% for the AUC and Cmax for all solid oral dosage forms, including HVDs, as long as two other criteria (the subject number and dissolution test results) are satisfied [16, 20]. When the second standard is employed, the PMDA requires dissolution similarity, except for ER drug products, for which dissolution equivalency is required. The PMDA consider appropriate evaluation to be possible using the combined results of human studies and dissolution tests conducted using three test fluids for IR and DR drug products and five test fluids for ER drug products with different stirring speeds. HC maintains that the GMR for Cmax should lie within 80.0–125.0% rather than the 90% CI, because Cmax is generally a more variable parameter and HC does not consider it necessary to constrain acceptance around it. However, for CDD products, HC allows 90% CIs for both parameters for fasted and fed conditions, but the acceptance range is different for the AUC and Cmax. The acceptance range for the 90% CI is decreased to 90.0–112.0% for AUC and 80.0–125.0% for Cmax. With respect to NTID products, the US FDA and the European Medicines Agency (EMA) also adopt the narrower range. We recommend Japan consider the narrower acceptance range for NTID products.

Regarding HVD products, HC adopts a reference-scaled average bioequivalence approach like the US FDA and EMA, but the acceptance criteria varies among different countries and regions [20, 21]. HC adopts this approach for AUC only, whereas the US FDA accepts it for the AUC and Cmax, and the EMA allows it for Cmax only. On the other hand, HC allows the GMR for Cmax for HVD products. HC recommends conducting fasted and fed bioequivalence studies for MR drug products. It is the opinion of the authors that more attention is given to the evaluation of HVDs.
of MR products than to IR products because MR products have additional complexity related to drug release. Therefore, for DR drug products, Japan should consider bioequivalence studies conducted in both fed and fasted states.

Finally, we compared the published guidelines, guidelines, and basic principles for bioequivalence and bio waivers. Both authorities published the guideline or guidance for dermatological dosage forms. However, some evaluation methods differed [33], the major difference being that the PMDA accepts dermatopharmacokinetic tests that compare the concentration level in the stratum corneum [22]. The PMDA and HC have basic principles or guidance with respect to inhalation products, and both authorities require in vitro, pharmacokinetic, and pharmacodynamic or clinical endpoint studies to evaluate the equivalency between generic and innovator products (HC considers biowaivers only in the case of aqueous solutions for inhalation). The main differences are that HC recommends setting placebo arms in place, in addition to generic and innovator products, in pharmacodynamic or clinical endpoint studies to confirm assay sensitivity, and that sputum eosinophil counts should be the primary endpoint for inhaled corticosteroids. Regarding primary endpoints, the PMDA currently recommends using the trough forced expiratory volume in 1 s (FEV$_1$) change from baseline, the morning peak expiratory flow (PEF) change from baseline, and the FEV$_1$-AUC$_{0-\infty}$ change from baseline, and so on, for orally inhaled dry powder drug products. The authors recommend that Japan develop documents for bioequivalence studies for nasal drug products for the treatment of allergic rhinitis, for the quality aspects of orally inhaled drug products, and for bio waivers related to aqueous solutions and the biopharmaceutics classification system.

5 Conclusions

We surveyed generic drug reviews in Japan and Canada. The survey describes many similarities and differences and highlights areas for improvement that could be considered to promote better generic drug reviews. In particular, we recommend the Japanese authorities proceed with the use of e-CTD to promote efficient review, produce generic drug review reports to ensure transparency of reviews, and develop documentation for bioequivalence and bio waiver evaluations of various dosage forms to promote efficient development. We hope to consider bioequivalence evaluations for nasal products and bio waivers for aqueous solutions with intramuscular or subcutaneous injections in the near future. Additionally, HC may consider requiring generic companies to assure complete interchangeability of all strengths marketed by the innovator, similar to that required in Japan. These results clarify the future challenges of generic drug reviews, and the similarities and differences found will also be important considerations for the future. We believe these challenges will lead to better regulations, and will benefit the aging population in both countries. This is the first article to discuss and clarify differences between and the similarities of generic drug reviews in Japan and Canada.

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Compliance with Ethical Standards

Conflict of interest Ryosuke Kuribayashi and Scott Appleton have no conflicts of interest that might be relevant to the contents of this manuscript.

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