**Appendix 4. Rationale for covariate definitions**

- The 1st level of the World Health Organization Anatomic Therapeutic Chemical (ATC) classification system: if the number of molecules in one ATC class was ⩽5 in any policy period, the ATC class was not considered as a separate category and was combined into "other ATC".
- The number of comparators in Canada was defined as the number of molecules within the same ATC level 4 sold in Canada in the quarter of the global first launch, and then categorized into 0, 1-4 and >4 to indicate the availability of drugs for therapeutic class comparison test conducted by the PMPRB and the potential therapeutic advance in Canada. The PMPRB's Human Drug Advisory Panel (HDAP), who provides expertise and advice to PMPRB staff, uses ATC level 4 to select drug products for their Therapeutic Class Comparison test and the level of therapeutic improvement according to the Guidelines (https://www.pmprb-cepmb.gc.ca/view.asp?ccid=492#1639). Breakthrough was defined as "*no drug products recommended by HDAP for comparison purposes for a new patented drug product that represents a breakthrough, given that such a drug product is, by definition the first one to be sold in Canada that treats effectively a particular illness or addresses effectively a particular indication*." In addition, in literature, the me-too drugs or follow-on drugs are defined relative to the first-in-class drug or breakthrough drug in the same therapeutic class (Aronson and Green 2020 and Andrade et al. 2016). For example, Andrade et al. (2016) used the ATC level 4 to define first-in-class and follow-on drugs. Thus, we think the number of molecules within the same ATC level 4 sold in Canada would be a good indicator of the level of therapeutic improvement. The 0 category indicates the molecules were breakthrough or first-in-class drug in Canada. However, other than 0, we are not aware of any existing meaningful cutoff that can inform our categorization. We finally chose the cutoff based on our data distribution (i.e, the third quartile among all study molecules = 5) to indicate the molecules that had more comparators in Canada. Therefore, the final three categories were 0, 1-4, and >4.
    - Aronson JK, Green AR. Me‐too pharmaceutical products: History, definitions, examples, and relevance to drug shortages and essential medicines lists. Br J Clin Pharmacol. 2020 Nov;86(11):2114–22.
    - Andrade LF, Sermet C, Pichetti S. Entry time effects and follow-on drug competition. Eur J Health Econ. 2016 Jan;17(1):45–60.
- High price was defined as whether the average price per standard unit of the first globally launched molecule within the first year was in the top 10% among all existing Innovative Branded molecules in the corresponding launching country and time. Previous studies found that higher prices or higher expected prices were associated with higher availability of medicines or faster time to launch. However, it is difficult to define high-priced molecules because the molecules could be launched in different countries at different launching timing, and their prices might not be comparable. We therefore defined "high price" based on the price ranking in the first launching country at the corresponding launching time. For example, if a molecule was first launched in the US, we defined the ranking of its price among the prices of all the existing innovative branded molecules in the US at the launching time. The cutoff of top 10% was chosen to represent highly priced molecules. The following reports from the Office of the Assistant Secretary for Planning and Evaluation, U.S.

Department of Health and Human Services have also used the same top 10% cutoff to define highly priced drugs in the US.
    - https://aspe.hhs.gov/reports/competition-prescription-drug-markets
    - https://aspe.hhs.gov/sites/default/files/documents/88c547c976e915fc31fe2c6903ac0bc9/sdp-trends-prescription-drug-spending.pdf
- Expected market size was indicated by the first-year sales in the US. Most molecules were launched in the US and thus the sales in the US could represent an expected market size for each individual country consistently. Considering the required follow-up time for our study molecules, the first-year duration was chosen. The cutoff of US$20M was chosen to balance the sample size for each category as well as the definition of high market size (>CAN$50M annually) in the proposed PMPRB guidelines on October 23, 2020. The PMPRB research webinar (2020) indicated that 25% of the patented medicines realize over CAN$23M and CAN$49M in annual sales by the third year and tenth year in Canada.
    - Patented Medicine Prices Review Board. PMPRB Guidelines. Published October 23, 2020. Accessed March 9, 2021. https://www.canada.ca/en/patented-medicine-prices-review/services/legislation/about-guidelines/guidelines.html
    - Berger J, Yang J. Insight into the spending on expensive drugs for rare diseases and the market size of patented medicines in Canada [Internet]. PMPRB Research Webinar presented at: PMPRB Research Webinar; 2020 Jun 23 [cited 2020 Jul 10]; Ottawa. Available from: https://www.canada.ca/content/dam/pmprb-cepmb/documents/consultations/draft-guidelines/2020/Research-Webinar1-EDRD-Market-Size-EN.pdf