Supplemental Online Content

Feldman WB, Tu SS, Alhiary R, Kesselheim AS, Wouters OJ. Manufacturer revenue on inhalers after expiration of primary patents, 2000-2021. *JAMA*. Published January 3, 2023. doi:10.1001/jama.2022.19691

eMethods

This supplemental material has been provided by the authors to give readers additional information about their work.

eMethods

Cohort identification

We excluded over-the-counter inhalers from our cohort. One such product, Primatene Mist (epinephrine), was approved during the study period.

Expiration dates of patents

All patents listed in the Food and Drug Administration's (FDA) Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book) through the 2021 edition were analyzed when determining the expiration dates of last-to-expire patents. Expiration dates reflected 6-month pediatric extensions, where relevant. Expiration dates of primary patents were considered "pre-approval" when no patents on the active ingredients in a given inhaler line were listed in the Orange Book during the study period. In some cases, such patents had been listed on earlier products in the Orange Book but had subsequently expired before the study period; in other cases (for example, older products like glycopyrrolate, which was first approved in 1961), no patents on the active ingredients were listed in the Orange Book.

Device hops

"Device hops" refer to instances in which a brand-name inhaler manufacturer releases a new product with the same active ingredient(s) as an older product but in a new delivery device. The originator and follow-on products (which together constitute a single inhaler line) have identical primary patents since they contain the same active ingredients, but their secondary patents may differ. Device hops allow inhaler manufacturers to obtain secondary patents on follow-on products that expire later than secondary patents on originators and thereby extend their revenue streams on inhaler lines. Our analysis analyzed all revenue earned on inhaler lines when primary patents were active. We then compared this to revenue earned on inhaler lines after primary patent expiration when secondary patents were active on at least one product in the inhaler line.

Imputed revenue data

In some cases, manufacturers provided US revenue for certain years but not others. When data on US revenue were missing for a given year but the historic ratio of US to global revenue for that product could be determined (using at least 5 consecutive data points), we imputed US revenue based on global revenue. When data on US revenue for a given product were missing and the

historic ratio of US to global revenue for that product could not be determined, we used linear interpolation (when 5 consecutive data points were present or, if there were fewer than 5 years of follow-up, data on > 65% of follow-up time were present). When neither method could be used to impute US revenue data, we left the data field blank.

Generic competition

Generic competitors may challenge patents listed in the Orange Book (in what are called “Paragraph IV certifications”), and thus brand-name drugs sometimes face generic competition before FDA-listed patents expire. In a sensitivity analysis, we quantified how much revenue was earned on inhaler lines with active secondary patents facing generic competition versus how much revenue was earned on inhaler lines with active secondary patents lacking generic competition.