Supplemental Online Content

Egilman AC, Van de Wiele VL, Rome BN, et al. Frequency of approval and marketing of biosimilars with a skinny label and associated medicare savings. *JAMA Intern Med*. Published online November 28, 2022. doi:10.1001/jamainternmed.2022.5419

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

eMethods

Sample Identification

Using publicly available FDA data,[1,2] we identified biosimilars approved through December 31, 2021 and compared their original labels to the label of their corresponding originator biologic at the time of biosimilar approval. We distinguished cases in which the biosimilar initially received approval for all (full label) versus only some (skinny label) of the originator biologic's indications. The FDA generally requires biosimilar manufacturers to demonstrate clinical equivalence in a comparative trial for at least 1 indication of the originator biologic and then extrapolates efficacy to other indications based on the consideration of many factors.[3,4] We reviewed FDA action package documents, including medical and summary reviews, to ensure the FDA extrapolated all indications sought by biosimilar manufacturers, so that the only indications omitted from skinny labels were intentionally carved out by the biosimilar manufacturer.

We then compared biosimilar and originator biologic supplementary labels to identify any additional carved out indications, including supplemental indications acquired by originator biologics after the initial biosimilar approval. For skinny label biosimilars, we determined when carved out indications were added to the biosimilar label through December 31, 2021. Since there can be long delays between when biosimilars are approved and marketed, we also evaluated whether each biosimilar had a full or skinny label at the time of marketing. We determined the date of biosimilar market entry using public data from the Medicaid Drug Rebate Program.[5]

Identification of Patents and Regulatory Exclusivities

To identify patents protecting carved-out indications, we used the patent database, Espacenet.[6] We combined key words from the carved-out indication (e.g., arthritis) with the originator molecule's non-proprietary name (e.g., adalimumab) in our search, applying the following two filters: patents or patent applications only and name of the originator biologic manufacturer (and its subsidiaries) only. One investigator (VW) examined the claims of each identified patent, forwarding possibly relevant patents to a second investigator (AE), who reviewed each patent to determine whether it could reasonably be asserted to protect a carved-out indication (**SA2**).[7,8] Patents believed to meet this criterion were then independently examined by a third examiner (AS), with disagreements resolved by consensus. To verify the robustness of the Espacenet search, we conducted a similar query of two additional databases—the United States Patent and Trademark Office (USPTO) Patent Full-Text and Image database and the USPTO Patent Application Full-Text and Image database[9,10]—using the originator biologics pegfilgrastim (Neulasta, Amgen) and ranibizumab (Lucentis, Genentech).

Two regulatory exclusivities that would otherwise prevent FDA from approving biosimilars may be subject to labeling carve outs. These are the 7-year orphan drug exclusivity, provided to manufacturers of drugs that treat a rare disease, and the 3-year new clinical investigation exclusivity, granted to manufacturers for completing studies essential to the approval of new indications, patient populations, or dosing regimens.[11] We searched FDA's Orphan Drug Product Approvals database to identify any orphan exclusivities protecting carved out indications.[12] We reviewed the supplemental approval

letters of originator biologics and FDA review documents to identify any new clinical investigation exclusivities covering carved out indications.

Period of Competition from Skinny Label Biosimilars

To determine the time originator biologics experienced competition due to skinny labeling, we measured the time from the launch of the first skinny label biosimilar to either the date of first full label biosimilar approval, the latest expiration date among patents and regulatory exclusivities protecting their carved-out indications (i.e., when a biologic became eligible for a full-label biosimilar), or through December 31, 2021, whichever was earlier. We also projected the time originator biologics would be subject to potential competition due to skinny labeling by measuring to the date an originator biologic had a full-label biosimilar approved or became eligible for a full-label biosimilar, rather than using December 31, 2021 as the cutoff date. Although patents often outlast regulatory exclusivities, they can be challenged and invalidated in litigation.[13-16] We therefore conducted a secondary analysis using only the latest expiration date of regulatory exclusivities protecting carved-out indications.

Medicare Savings

In cases we identified regulatory exclusivity or patent protection of the carved-out indications (**SA3**), we estimated savings from earlier biosimilar competition during the period between first marketing of a skinny label biosimilar and the date of first approval or eligibility of a full label biosimilar, or December 31, 2020, whichever was earlier. The originator biologics facing competition from skinny label biosimilars were all clinician-

administered medications and primarily reimbursed through Medicare Part B, which sets reimbursement rates at the average sales price paid by commercial insurers net of rebates and discounts.[17]

Using publicly available data from the Medicare Part B Drug Spending Dashboard,[18] we estimated savings by comparing actual Medicare Part B spending on originator biologics and their skinny label biosimilars with estimated spending had skinny labeling not been available. To estimate Medicare spending had no skinny label biosimilar been marketed, we calculated each originator biologic's compound annual growth rate in average spending per dosage unit (i.e., price) during the five-years prior to competition by the first skinny label biosimilar. We assumed originator biologics would continue to increase in price at this pre-competition rate until a full-label biosimilar was approved or eligible. We multiplied the projected annual price of the originator biologic by the actual annual dosage units of the originator biologic and its skinny label biosimilars. We pro-rated annual data in cases when skinny label biosimilars were marketed for only part of a year or an originator biologic had a full-label biosimilar approved or become eligible prior to 2020, assuming equal use across the calendar year. Since lower prices from biosimilar competition may have increased use, we conducted a sensitivity analysis using the volume and price of the originator biologic in the last full year before biosimilar competition to project Medicare spending had a skinny label biosimilar not been marketed.

To account for inflation, all prices were converted to 2021 US dollars using the Consumer Price Index for All Urban Consumers. This study was not submitted for institutional review board approval because it used public, nonidentifiable data and did not constitute human subjects research.

eTable 1. Rules for Assessing Whether a Patent is Protective of a Carved-Out Indication

1. Only method of use claims were considered based on the premise that if valid, other categories of claims (e.g., composition, manufacturing, etc.) would protect all uses and thus would not be susceptible to skinny labeling.
2. Claims that list a carved-out indication together with other US Food and Drug Administration (FDA) approved non-carved-out uses were not considered protective unless specific or unique claims to the carved-out use were also made. This determination was based on the premise that if valid, the claims would have also precluded biosimilar approval and marketing for the other non-carved out uses, which they did not (e.g., claim 29 in patent US9085618B2 for adalimumab and claims 31 and 38 in patent US10072075B2 for ranibizumab).
3. Patents with narrower claims than the carved-out indication were considered protective if they would block a substantial amount of the product's use. This determination was based on a review of scientific literature, information available in FDA labels, UpToDate, and our best clinical judgement. In certain instances, we consulted with colleagues in other specialties to determine whether a use claim would preclude substantial use (e.g., claim 1 in patent US2021015901A1 on using pegfilgrastim in combination with romiplostim to treat patients acutely exposed to myelosuppressive doses of radiation was considered protective).
4. If the claims did not specifically mention a pediatric patient population that was carved out but used broader terms, such as humans, subjects, patients, that encompass pediatric age groups and use for the adult population was also carved out, then we considered the claims protective (e.g., patent US8747854B2 for adalimumab).
5. Claims covering the use of an indication originally carved out by a biosimilar, but subsequently added to the same biosimilar's label during the remaining life of the patent were not considered protective (e.g., patent US8778340B2 for bevacizumab). Similarly, claims covering the use of an indication carved out by one biosimilar and not carved out by another biosimilar within the patent's term remaining life were not considered protective (e.g., patent US7682612B1 rituximab covering use for chronic lymphocytic leukemia. Its biosimilar, rituximab-pvvr, was approved with the chronic lymphocytic leukemia indication prior to expiration of the '612B1 patent).

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