California Health Benefits Review Program

Analysis of California Senate Bill 1452
Biological Products

A Report to the 2019–2020 California State Legislature

May 21, 2020

CALIFORNIA
HEALTH BENEFITS REVIEW PROGRAM

Key Findings

Analysis of California Senate Bill 1452 Biological Products

Summary to the 2019–2020 California State Legislature, May 21, 2020

AT A GLANCE

The version of California Senate Bill (SB) 1452 analyzed by CHBRP states that *if* health plans and policies provide coverage for reference biologics or the respective biosimilars under the medical benefit, plans and policies cannot limit which manufacturer's products are to be used when medically necessary.

1. CHBRP estimates that, in 2020, of the 21.7 million Californians enrolled in state-regulated health insurance, 100% of them will have insurance subject to SB 1452, including Californians in Medi-Cal managed care plans.
2. **Benefit coverage.** Approximately 68% of enrollees enrolled in commercial plans and policies, 72% of enrollees in CalPERS plans, and 0% of enrollees in Medi-Cal managed care plans have coverage that is fully compliant with SB 1452 at baseline.
3. **Utilization.** Due to lack of data, CHBRP is unable to estimate utilization of reference biologics and their biosimilars.
4. **Medical effectiveness findings:**
   a. *Limited evidence* that that biosimilars covered under the medical benefit are as safe as the reference biologics due to a lack of published studies of some biosimilars.
   b. *Insufficient evidence* that prior authorization and step therapy affect utilization of reference biologics and their biosimilars or health outcomes.
5. **Public health.** The public health impact of SB 1452 is unknown due to insufficient evidence regarding the impact of prior authorization and step therapy protocols on the utilization and cost of biologics or biosimilars. Thus, the impact of SB 1452 on disparities are also unknown.

CONTEXT

Biologics, or biological products, are preparations made from living organisms used to prevent, diagnose, treat, and cure a wide range of diseases and medical conditions.[1] Common examples include influenza and shingle vaccines, Avastin, and Humira. Most biologics are administered through intravenous infusion or subcutaneous or intramuscular injection. Those that require intravenous infusion are administered by a health professional and may be covered under an enrollee's medical benefit. Subcutaneous biologic injections may be self-administered by the patient with approval from a provider. Newer biologics are also administered through inhalers.

A biosimilar, or follow-on biologic, is a biologic with a highly similar structure and function to a reference product that does not demonstrate clinically meaningful differences in terms of purity, chemical identity, and bioactivity. The FDA approved the first biosimilar in March 2015. While biosimilars are versions of brand-name products, they are not the same as generic medications because they are not exact replicas of the reference product.

Biologics and biosimilars treat a wide range of conditions. Breast cancer, Non-Hodgkin's lymphoma, and numerous other types of cancers are some of the more common conditions treated with biologics typically covered under the medical benefit.

BILL SUMMARY

If health plans and policies provide coverage for "biological products" or the respective biosimilars under the medical benefit, SB 1452 states that plans and policies cannot limit which manufacturer's biological products or biosimilars are to be used when medically necessary. This provision is specific to physician- or clinician-administered biological products or the respective biosimilars.

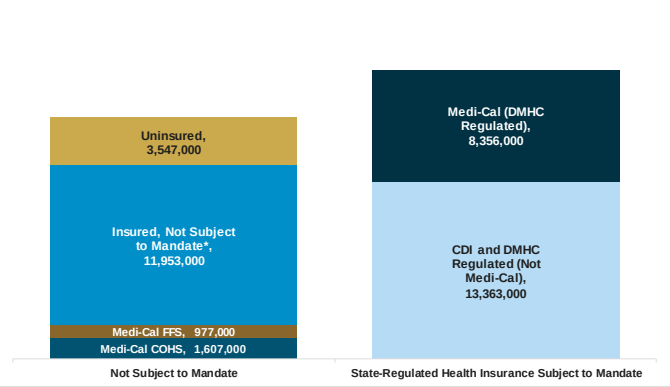
SB 1452 also prohibits plans and policies from requiring prior authorization or step therapy requirements that limit which manufacturer's biological products or the

[1] Refer to CHBRP's full report for full citations and references.

respective biosimilars are to be administered by a physician or clinician to an enrollee.

SB 1452 only applies to reference biologics and biosimilars covered under the medical benefit. SB 1452 would not affect coverage for biologics and biosimilars that are covered under the pharmacy benefit. Additionally, while prior authorization and step therapy are prohibited when these policies require clinicians to use one biologic or biosimilar over another equivalent product, SB 1452 does not prohibit prior authorization or step therapy related to medical necessity or clinical appropriateness of a medication.

Figure A. Health Insurance in CA and SB 1452



Source: California Health Benefits Review Program, 2020.

Notes: *Medicare beneficiaries, enrollees in self-insured products, etc.

IMPACTS

Benefit Coverage, Utilization, and Cost

CHBRP provides a qualitative discussion of the potential impacts to benefit coverage, utilization, and cost because CHBRP's quantitative data sources do not include data on any of the biosimilars that entered the market after 2017. CHBRP provides in this section an overview of baseline compliance with SB 1452 based on CHBRP's survey of health insurance plans and policies and a short discussion regarding the potential utilization and cost impacts of the bill based on the literature.

Benefit Coverage

Approximately 68% of enrollees in commercial plans and policies, 72% of enrollees in CalPERS plans, and 0% of enrollees in Medi-Cal managed care plans have coverage that is fully compliant with SB 1452 at baseline. Full compliance was defined as being compliant for all of the following three provisions: (1) coverage of all physician- and clinician-administered biosimilars and their associated reference biologic[2], (2) no prior authorization for the covered reference biologics and its biosimilars related to medication choice, and (3) no step therapy for the covered reference biologics and its biosimilars related to medication choice. Plans and policies could still have prior authorization and step therapy requirements for medical necessity as long as the requirements were applied equally to all covered reference biologics and biosimilars.

Postmandate, 100% of enrollees would have coverage fully compliant with SB 1452.

Prior Authorization and Step Therapy

While Medi-Cal managed care plans have greater coverage for the reference biologics and biosimilars (86% of enrollees in such plans have compliant coverage based on coverage of the medications) compared to enrollees in commercial or CalPERS plans and policies, coverage for the majority of enrollees in Medi-Cal managed care plans includes prior authorization to access certain medications. Thus, prior authorization was the main driver of noncompliance with SB 1452 at baseline for enrollees in Medi-Cal managed care plans. In contrast, enrollees in commercial plans and policies have the lowest levels of coverage of the medications (71% of enrollees in commercial plans and policies were deemed compliant based on coverage) for all reference biologics and biosimilars compared to enrollees in CalPERS and Medi-Cal managed care plans, but the vast majority of enrollees were in plans and policies that have no prior authorization requirements (86%) to access certain medications that are covered. Most enrollees in CalPERS plans have coverage with no prior authorization to access certain medications (96% compliance) and only a share of enrollees have coverage that was noncompliant based on coverage of medications and step therapy.

Baseline Utilization and Per-Unit Cost

Due to lack of available data, CHBRP is unable to determine utilization of reference biologics and their biosimilars.

In contrast to small molecule generic medications (i.e., medications that contain the same chemical substance as a branded medication), which can be upwards of 80% less expensive than their brand-name counterparts, biosimilars are anywhere between 15% and 40% less expensive than their biologic counterparts. Some

[2] Plans and policies are not required to cover all biologics and biosimilars, but if at least one reference biologic or the biosimilar is covered, all medications within that specific medication line need to be covered in order to be compliant.

enrollees are required to contribute a coinsurance for the medication that was administered to them in office, along with a copay or coinsurance for the office visit. The medication coinsurance amount is calculated based on the list price of the medication, which is the price usually published by the manufacturer and is available to the public.

Potential Postmandate Changes in Utilization and Cost

CHBRP lacks data needed to predict how SB 1452 would change utilization of biologics and biosimilars and how this would impact expenditures and enrollee out-of-pocket expenses. Apart from the lack of data, CHBRP concludes that due to the high degree of uncertainty in how the various stakeholders (health plans and insurers, providers, enrollees) impacted by this bill would react, the overall impact of this bill on utilization and expenditures is unknown.

- Health plans and insurers: While biosimilars are often listed at a discounted price in comparison to reference biologics, arrangements made by pharmacy benefit managers to secure rebates and other concessions that reduce the cost of reference biologics for payers may have limited the uptake of biosimilars. With SB 1452, plans and policies would not be able to explicitly prefer a reference biologic or a particular biosimilar over another. However, it is possible plans and payers could limit incentives to use the most expensive biologic products in other ways.

- Providers: While it is possible providers would shift towards preferring the lowest cost biosimilar for their patients, it is also possible providers opt to use more expensive products that would be more profitable to their practices.

- Enrollees: By prohibiting preference of one reference biologic or its biosimilar over another by health plans and insurers, SB 1452 could increase utilization of biosimilars. If an increased number of lower-cost biosimilars are utilized, enrollee cost sharing could be reduced. Enrollees may prefer lower-cost biosimilars over more expensive reference products. However, should providers switch to prescribing the reference biologic over its biosimilar, cost sharing for enrollees could increase or remain the same.

Medical Effectiveness

CHBRP assessed the safety of physician- and clinician-administered biosimilars (i.e., those typically covered under the medical benefit) compared to their reference biologics and the effect of prior authorization and step therapy requirements on utilization of these reference biologics and biosimilars and health outcomes.

There is limited evidence[3] that physician- and clinician-administered biosimilars are as safe as their reference biologics. CHBRP considered the evidence limited because most of the studies that CHBRP identified addressed reference biologics/biosimilars used to treat inflammatory diseases; few published studies addressed reference biologics/biosimilars used to treat cancer. Across the 11 articles included in the *Medical Effectiveness* section of the analysis, six examined the safety of biosimilars among mixed populations of people who were previously treated with a reference biologic or were not previously treated and five studied the safety of biosimilars among patients who switched from reference biologics. Most of these studies assessed the safety of infliximab (Remicade) biosimilars (most notably CT-P13, or infliximab-dyyb/Inflectra), but other studied biosimilars included filgrastim (Neupogen) biosimilars, trastuzumab (Herceptin) biosimilars, and rituximab (Rituxan) biosimilars. The studies consistently found that rates of adverse events were similar between patients treated with reference biologics and biosimilars.

There is insufficient evidence[4] that prior authorization and step therapy affect biologic/biosimilar utilization or health outcomes. CHBRP did not identify any studies that directly addressed this topic. A few studies address prior authorization or step therapy for reference biologics, but they do not examine the impact of these policies on utilization of biosimilars of these reference biologics or on health outcomes.

Public Health

Biologics and biosimilars treat a wide range of medical conditions and therefore the measurable health outcomes relevant to SB 1452 are dependent on both the treatment and condition in question. A significant change in utilization of these products could have an

[3] *Limited evidence* indicates that the studies have limited generalizability to the population of interest and/or the studies have a fatal flaw in research design or implementation.
[4] *Insufficient evidence* indicates that there is not enough evidence available to know whether or not a treatment is effective, either because there are too few studies of the treatment or because the available studies are not of high quality. It does not indicate that a treatment is not effective.

impact on the physical health outcomes of enrollees being treated by them.

In the first year postmandate, the public health impact of SB 1452 is unknown due to insufficient evidence regarding the impact of prior authorization and step therapy protocols on the utilization and cost of biologics or biosimilars. Thus, the impact of SB 1452 on disparities are also unknown. Please note that the absence of evidence is not "evidence of no effect." It is possible that an impact — desirable or undesirable — could result, but current evidence is insufficient to inform an estimate.

Long-Term Impacts

CHBRP lacks the data necessary to make conclusive statements on long-term impacts. This is due to insufficient evidence related to use and impact of prior authorization and step therapy for these drugs, and insufficient data related to their costs and utilization. Research efforts on biologics and biosimilars will likely continue for the foreseeable future and may impact the prescription drug market. However, it is unknown how these changes may influence the impacts of SB 1452 in the long-term.

Essential Health Benefits and the Affordable Care Act

SB 1452 would not require coverage for a new state benefit mandate. Instead, SB 1452 modifies terms and conditions of already covered medications. Therefore, SB 1452 appears not to exceed the definition of EHBs in California.

At the time of this CHBRP analysis, there is substantial uncertainty regarding the impact of the COVID-19 pandemic on premium rates and health plan enrollment, including how the pandemic will impact healthcare costs in 2021. Because the variance of potential outcomes is significant, CHBRP does not take these effects into account as any projections at this point would be speculative, subject to federal and state decisions and guidance currently being developed and released. In addition, insurers', providers', and consumers' responses are uncertain and rapidly evolving to the public health emergency and market dynamic.

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The California Health Benefits Review Program (CHBRP) was established in 2002. As per its authorizing statute, CHBRP provides the California Legislature with independent analysis of the medical, financial, and public health impacts of proposed health insurance benefit-related legislation. The state funds CHBRP through an annual assessment on health plans and insurers in California.

An analytic staff based at the University of California, Berkeley, supports a task force of faculty and research staff from multiple University of California campuses to complete each CHBRP analysis. A strict conflict-of-interest policy ensures that the analyses are undertaken without bias. A certified, independent actuary helps to estimate the financial impact. Content experts with comprehensive subject-matter expertise are consulted to provide essential background and input on the analytic approach for each report.

More detailed information on CHBRP's analysis methodology, authorizing statute, as well as all CHBRP reports and other publications, are available at www.chbrp.org.

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POLICY CONTEXT

The Senate Committee on Health has requested that the California Health Benefits Review Program (CHBRP)[5] conduct an evidence-based assessment of the medical, financial, and public health impacts of Senate Bill (SB) 1452, biological products. SB 1452 was amended on April 17, 2020, and CHBRP has been asked to analyze the language as amended.

Bill-Specific Analysis of SB 1452, Biological Products

Bill Language

If health plans and policies provide coverage for "biological products" or the respective biosimilars under the medical benefit, SB 1452 states that plans and policies cannot limit which manufacturer's biological products or biosimilars are to be used when medically necessary. This provision is specific to physician- or clinician-administered biological products or the respective biosimilars.

SB 1452 also prohibits plans and policies from requiring prior authorization or step therapy that limit which manufacturer's biological products or the respective biosimilars are to be administered by a physician or clinician to an enrollee.

The California Department of Insurance (CDI) and Department of Health Care Services (DHCS) both noted there is a possible reading of the bill language that would require coverage for all biologics and biosimilars, regardless if the biologic has a biosimilar. This would substantially expand the number of medications SB 1452 would require plans and policies to cover.

The full text of SB 1452 can be found in Appendix A.

Definitions included in SB 1452

Biological products are defined as a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.[6] Biological products are also called biologics, reference biologics, or originators.

Biosimilars are products that are highly similar to the reference biologic, notwithstanding minor differences in clinically inactive components, and there are no clinically meaningful differences between the biosimilar and the reference biologic in terms of safety, purity, and potency.[7]

Physician- or clinician-administered biological products or the respective biosimilars means medications that are administered by a healthcare provider or a clinician in a hospital, clinic, infusion center, their office, or other health care facility setting.

More information about biologics and biosimilars and where these medications are administered is included in the *Background on Biologics, Biosimilars, and Utilization Management Techniques* section.

[5] CHBRP's authorizing statute is available at www.chbrp.org/faqs.php.
[6] Section 262(i)(1) of Title 42 of the United States Code
[7] Section 262(i)(2) of Title 42 of the United States Code

Relevant Populations

If enacted, SB 1452 would affect the health insurance of approximately 21.7 million enrollees (55% of all Californians). This represents 100% of the 21.7 million Californians who will have health insurance regulated by the state that may be subject to any state health benefit mandate law — health insurance regulated by the California Department of Managed Health Care (DMHC) or the California Department of Insurance (CDI). If enacted, the law would affect the health insurance of enrollees in DMHC-regulated plans and CDI-regulated policies, including enrollees in CalPERS HMO products and Medi-Cal managed care plans.

Analytic Approach and Key Assumptions

CHBRP uses the following term throughout the report:

- "Reference biologics" refers to a biological product with biosimilars.

CHBRP makes the following assumptions for the purposes of this analysis:

- Plans and policies are not required to cover all biologics and biosimilars. SB 1452 only applies to reference biologics and their relevant biosimilars *if* a plan or policy currently provides coverage for them. If a plan or policy does not provide coverage for a reference biologic or its biosimilar, the plan or policy is not required to provide coverage for these medications. For example:
    - If a health plan or policy covers the reference biologic and biosimilar1 but not biosimilar2, to be compliant with SB 1452 the plan or policy would now need to cover biosimilar2 as well.
    - If a plan or policy covers biosimilar1 and biosimilar2 but not the reference biologic, to be compliant the plan or policy would now need to cover the reference biologic as well.
    - But if a plan or policy does not provide coverage for the reference biologic, biosimilar1 or biosimilar2, they would not be required to provide coverage for any of these medications.
- CHBRP assumes SB 1452 would require plans and policies to cover all biosimilars for a covered reference biologic. However, SB 1452 only requires plans and policies to "provide access to" the relevant biosimilars and does not explicitly state coverage is required.

SB 1452 only applies to reference biologics and biosimilars covered under the medical benefit. SB 1452 would not affect coverage for biologics and biosimilars that are covered under the pharmacy benefit.

While prior authorization and step therapy are prohibited when these policies require clinicians to use the reference biologic over its biosimilar(s) or the biosimilar(s) over the reference biologic, SB 1452 does not prohibit prior authorization or step therapy related to medical necessity and clinical appropriateness.

At the time of this CHBRP analysis, there is substantial uncertainty regarding the impact of the COVID-19 pandemic on premium rates and health plan enrollment, including how the pandemic will impact healthcare costs in 2021. Because the variance of potential outcomes is significant, CHBRP does not take these effects into account as any projections at this point would be speculative, subject to federal and state decisions and guidance currently being developed and released. In addition, insurers', providers', and consumers' responses are uncertain and rapidly evolving to the public health emergency and market dynamics.

Interaction With Existing Requirements

Health benefit mandates may interact and align with the following state and federal mandates or provisions.

California Policy Landscape

California law and regulations

California has an existing law regarding biologics and substitution of biosimilars if they have been designated as "interchangeable."[8] If biosimilars have been designated as such, a pharmacist can substitute a biosimilar for a prescribed biologic, as long as the patient's cost sharing is the same or lower than it would be for the prescribed biologic and the prescribing provider has not indicated substitution is not allowed. As of May 2020, no biosimilars have received the "interchangeable" designation. More information on "interchangeability" is included in the *Background on Biologics, Biosimilars, and Utilization Management Techniques* section.

California law requires coverage of treatment for various conditions, such as breast cancer.[9] However, the regulations do not specify which types of treatment fall under this requirement, such as treatment with a biologic or biosimilar.

California law includes time-specific requirements for a health plan or policy to respond to prior authorization and step-therapy requests for medications covered under the pharmacy benefit.[10] There is no corresponding requirement for medications covered under the medical benefit.

CHBRP is not aware of similar legislation to SB 1452 being introduced in California previously.

Similar requirements in other states

A similar bill to SB 1452 was introduced in Minnesota in January 2020. HF 3223 states that a pharmacy benefit manager or health carrier must not require or demonstrate preference for a pharmacy or health care provider to prescribe a reference biological product, a biosimilar for that reference product, or an interchangeable biological product. HF 3223 also states that if a pharmacy benefit manager or health carrier elects coverage of a product listed above, it must also elect equivalent coverage for all of the equivalent products (e.g., a biologic and the relevant biosimilars). One key difference between HF 3223 and SB 1452 is that HF 3223 applies to biologics and biosimilars covered under both the medical benefit and pharmacy benefit.

Federal Policy Landscape

Affordable Care Act

A number of Affordable Care Act (ACA) provisions have the potential to or do interact with state benefit mandates. Below is an analysis of how SB 1452 may interact with requirements of the ACA as presently exists in federal law, including the requirement for certain health insurance to cover essential health benefits (EHBs).[11,12]

For the 2020 plan year for nongrandfathered group plans and policies, the annual out-of-pocket maximums for an individual are $8,150 and $16,300 for a family.[13] This means once an enrollee or a

[8] Business and Professions Code 4073.5.
[9] H&SC 1367.6; IC 10123.8.
[10] H&SC 1367.241, 1367.244; IC
[11] The ACA requires nongrandfathered small-group and individual market health insurance — including but not limited to QHPs sold in Covered California — to cover 10 specified categories of EHBs. Policy and issue briefs on EHBs and other ACA impacts are available on the CHBRP website: www.chbrp.org/other_publications/index.php.
[12] Although many provisions of the ACA have been codified in California law, the ACA was established by the federal government, and therefore, CHBRP generally discusses the ACA as a federal law.
[13] HealthCare.gov. Out-of-pocket maximum/limit. Accessed on March 20, 2020. Available at https://www.healthcare.gov/glossary/out-of-pocket-maximum-limit/.

family hit these out-of-pocket maximums, they are no longer responsible for additional cost-sharing responsibilities for the remainder of the plan year. Enrollees using biologics or biosimilars typically have high-cost medical conditions and may be more likely to hit these out-of-pocket maximums.

Any changes at the federal level may impact the analysis or implementation of this bill, were it to pass into law. However, CHBRP analyzes bills in the current environment given current law and regulations.

The Biologics Price Competition and Innovation Act[14]

The Biologics Price Competition and Innovation Act (BPCIA) — a provision in the ACA — was signed into law in 2010. The stated purpose of the legislation is to establish "a biosimilars pathway balancing innovation and consumer interests." The BPCIA amends Section 351 of the Public Health Service Act to include an abbreviated process for the Food and Drug Administration (FDA) to approve follow-on versions of originator biological products. Additionally, the BPCIA details the information required for a biological product to be deemed biosimilar, introduces standards for determining interchangeability of a biosimilar and its reference product (i.e., instances in which a pharmacist may substitute a biosimilar for the reference product without the intervention of the health care provider who prescribed the reference product), and establishes a 12-year period of exclusivity for the initial reference product (i.e., before any biosimilar application may be approved) as well as an exclusivity period for the first biosimilar determined to be interchangeable with a particular reference product.

Essential Health Benefits

Nongrandfathered plans and policies sold in the individual and small-group markets are required to meet a minimum standard of benefits as defined by the ACA as essential health benefits (EHBs). In California, EHBs are related to the benefit coverage available in the Kaiser Foundation Health Plan Small Group Health Maintenance Organization (HMO) 30 plan, the state's benchmark plan for federal EHBs.[15,16] CHBRP estimates that approximately 4 million Californians (10%) have insurance coverage subject to EHBs in 2021.[17]

States may require plans and policies to offer benefits that exceed EHBs.[18] However, a state that chooses to do so must make payments to defray the cost of those additionally mandated benefits, either by paying the purchaser directly or by paying the qualified health plan.[19,20] Health plans and policies sold outside of the health insurance marketplaces are not subject to this requirement to defray the costs. State rules related to provider types, cost sharing, or reimbursement methods would not meet the definition of state benefit mandates that could exceed EHBs.[21] SB 1452 would not require coverage for a new state benefit mandate. Instead, SB 1452 modifies terms and conditions of already covered medications. Therefore, SB 1452 appears not to exceed the definition of EHBs in California.

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[14] ACA Section 7001-7003.
[15] CCIIO, Information on Essential Health Benefits (EHB) Benchmark Plans. Available at: https://www.cms.gov/cciio/resources/data-resources/ehb.html.
[16] H&SC Section 1367.005; IC Section 10112.27.
[17] CHBRP, *Estimates of Sources of Health Insurance in California in 2021*. Available at: www.chbrp.org/other_publications/index.php.
[18] ACA Section 1311(d)(3).
[19] State benefit mandates enacted on or before December 31, 2011, may be included in a state's EHBs, according to the U.S. Department of Health and Human Services (HHS). Patient Protection and Affordable Care Act: Standards Related to Essential Health Benefits, Actuarial Value, and Accreditation. Final Rule. Federal Register, Vol. 78, No. 37. February 25, 2013. Available at: https://www.gpo.gov/fdsys/pkg/FR-2013-02-25/pdf/2013-04084.pdf.
[20] However, as laid out in the Final Rule on EHBs HHS released in February 2013, state benefit mandates enacted on or before December 31, 2011, would be included in the state's EHBs, and there would be no requirement that the state defray the costs of those state-mandated benefits. For state benefit mandates enacted after December 31, 2011, that are identified as exceeding EHBs, the state would be required to defray the cost.
[21] Essential Health Benefits. Final Rule. A state's health insurance marketplace would be responsible for determining when a state benefit mandate exceeds EHBs, and QHP issuers would be responsible for calculating the cost that must be defrayed.

BACKGROUND ON BIOLOGICS, BIOSIMILARS, AND UTILIZATION MANAGEMENT TECHNIQUES

This section provides context for the consideration of the impacts of SB 1452 by defining biologics, biosimilars, and the utilization management techniques referred to in the legislation.

What Are Biologics and Biosimilars?

Biologics

Biologics, or biological products, are preparations made from living organisms used to prevent, diagnose, treat, and cure a wide range of diseases and medical conditions. They are typically large, complex molecules (~50,000 kilodaltons[22]) and may be composed of biomolecules, including carbohydrates, proteins, and nucleic acids, or whole cells and tissues (Dabrowska, 2019). Common examples include influenza and shingle vaccines, Avastin, and Humira. Most biologics are administered through intravenous infusion or subcutaneous or intramuscular injection. Those that require intravenous infusion are administered by a health professional and may be covered under an enrollee's medical benefit. Subcutaneous biologic injections may be self-administered by the patient with approval from a provider. Newer biologics are also administered through inhalers.

Biologics are regulated by the Food and Drug Administration (FDA). Unlike most small molecule medications (<1,000 kilodaltons), which are chemically synthesized and therefore have well-defined structures that are easy to characterize[23], biologics have natural variations that make them difficult to characterize and lead to differences between manufactured lots. During its review of a biologic, FDA examines the manufacturer's protocols and strategies to minimize product variations to ensure the biologic demonstrates consistent clinical performance (FDA, 2020). Biologics that are approved by the FDA for safety and effectiveness can become reference biologics, or comparisons, for biosimilars.

Biosimilars and Interchangeable Products

A biosimilar, or follow-on biologic, is a biologic with a highly similar structure and function to a reference biologic that does not demonstrate clinically meaningful differences in purity, chemical identity, and bioactivity. The FDA approved the first biosimilar in March 2015. While biosimilars are versions of brand-name products, they are not the same as generic medications because they are not exact replicas of the reference biologic. FDA-approved biosimilars and their associated reference biologics that may be covered under the medical benefit are shown in Table 1. Medications usually covered under the medical benefit include Avastin, Epogen/Procit, Herceptin, Neluasta, Neupogen, Remicade, and Rituxan and their biosimilars. Other reference biologics with biosimilars, such as Enbrel and Humira, are usually covered under an outpatient pharmacy benefit. As discussed in the *Policy Context* section, SB 1452 only requires health plans and policies to cover reference biologics and biosimilars that are clinician- or physician-administered, and therefore typically covered under the medical benefit.

Interchangeable products are biosimilars that meet additional requirements outlined in the federal Biologics Price Competition and Innovation Act (BPCIA). To be considered interchangeable, the BPCIA requires a biosimilar to produce the same clinical result as the reference biologic in any given patient. In addition, the biosimilar must be able to be substituted for the reference biologic without the need for intervention by the provider who prescribed the reference product. The FDA approved the guidelines for biosimilar interchangeability in May 2019 (FDA, 2019). To date, there are no FDA-approved interchangeable products on the market.

[22] A kilodalton is a unit of molecular mass or molecular weight. One kilodalton is equal to one kilogram per mole.
[23] Drug characterization is the determination of the chemical and physical properties of the product, including the molecule's size, shape, optimal conditions to maintain function, toxicity (Parr et al., 2016).

Table 1. Clinician-Administered Reference Biologics and Biosimilars Available and Conditions for Which They are Used

Reference Biologic Medication	Biosimilar(s)	Year Biosimilar Approved	FDA-Approved Indications for all Reference Biologics and Biosimilars*	How Medication Is Administered	Market Availability
Avastin (bevacizumab)	Mvasi (bevacizumab-awwb) Zirabev (bevacizumab-bvzr)	2017 2019	Cervical cancer Metastatic colorectal cancer Metastatic renal cell carcinoma Non-squamous non-small cell lung cancer Recurrent glioblastoma	Infusion administered by a health professional in a medical office, infusion center, or hospital	All available
Epogen/Procrit (epoetin alfa)	Retacrit (epoetin alfa-epbx)	2018	Anemia	Subcutaneous injection or intravenously; administered by health professional or patient	All available
Herceptin (trastuzumab)	Ogivri (trastuzumab-dkst) Herzuma (trastuzumab-pkrb) Ontruzant (trastuzumab-dttb) Trazimera (trastuzumab-qyyp) Kanjinti (trastuzumab-anns)	2017 2018 2019 2019 2019	Breast cancer Metastatic gastric or gastroesophageal junction adenocarcinoma (a)	Infusion administered by a health professional	All available except Ontruzant: availability unknown
Neulasta (pegfilgrastim)	Fulphila (pegfilgrastim-jmdb) Udenyca (pegfilgrastim-cbqv) Ziextenzo (pegfilgrastim-bmez)	2018 2018 2019	Febrile neutropenia	Subcutaneous injection or intravenously; administered by health professional or patient	All available

Reference Biologic Medication	Biosimilar(s)	Year Biosimilar Approved	FDA-Approved Indications for all Reference Biologics and Biosimilars*	How Medication Is Administered	Market Availability
Neupogen (filgrastim)	Granix (filgrastim-tbo) Zarxio (filgrastim-sndz) Nivestym (filgrastim-aafi)	2014 2015 2018	Neutropenia Severe neutropenia Febrile neutropenia Congenital neutropenia Cyclic neutropenia Idiopathic neutropenia Acute myeloid leukemia	Subcutaneous injection or intravenously; administered by health professional or patient	All available
Remicade (infliximab)	Inflectra (infliximab-dyyb) Renflexis (infliximab-abda) Ixifi (infliximab-qbtx) Avsola (infliximab-axxq)	2016 2017 2017 2019	Crohn's disease Pediatric Crohn's disease Ulcerative colitis Pediatric ulcerative colitis Rheumatoid arthritis Ankylosing spondylitis Psoriatic arthritis Plaque psoriasis	Infusion administered by a health professional	All available except Aysola and Ixifi
Rituxan (rituximab)	Truxima (rituximab-abbs) Ruxience (rituximab-pvvr)	2018 2019	Non-Hodgkin's lymphoma Chronic lymphocytic leukemia Rheumatoid arthritis (b) Granulomatosis with polyangiitis Microscopic polyangiitis	Infusion administered by a health professional	All available

Source: California Health Benefits Review Program, 2020.

Notes: *Unless otherwise indicated. (a) Metastatic gastric or gastroesophageal junction adenocarcinoma is not an FDA-approved indication for Herzuma. (b) Rheumatoid arthritis is not an FDA-approved indication for Ruxience.

Key: FDA = Food and Drug Administration

Prevalence of Diseases Treated by Biologics and Biosimilars in California

Biologics and biosimilars treat a wide range of conditions. The prevalence of their use depends on the ailment that is being treated. Rheumatoid arthritis, Crohn's disease, and numerous types of cancers are some of the more common conditions treated with biologics, as indicated in Table 1. Biologics and biosimilars used to treat some cancers, such as breast cancer and Non-Hodgkin's lymphoma, are typically covered only under the medical benefit whereas biologics and biosimilars used to treat other conditions, such as rheumatoid arthritis and Crohn's disease, can be covered under either the medical or outpatient pharmacy benefit. Rheumatoid arthritis is an autoimmune and inflammatory disease that affects 1.3 million people nationally (CDPH, 2017). Crohn's disease and ulcerative colitis are inflammatory bowel diseases that impact about 3 million people nationwide. In California, breast and colorectal cancers are the second and third leading causes of cancer death in women, occurring in 121.23 and 31.03 per 100,000 persons, respectively. Colorectal cancer is also the third leading cause of cancer death in men in California, with an incidence rate of 39.25 per 100,000 males (CCR, 2017). Non-Hodgkin's lymphoma occurs in 21.4 per 100,000 persons in California (Movsisyan et al., 2019).

Factors that Promote or Prohibit Utilization of Biosimilars

In the United States, fewer than 2% of Americans use biologics, yet it is estimated these drugs account for around 40% of all pharmaceutical spending (Mulcahy et al., 2018; Zhai et al., 2019). With sales reaching between $5.1 and nearly $20 billion, biologics were 11 out of the top 15 selling drugs in the United States in 2018 (Dabrowska, 2019). From 2014 to 2018, spending on biologic drugs increased 50% to $125 billion (Brill and Ippolito, 2019). Research suggests that the increase in spending is driven primarily by the increase in prices of these products, not simply due to increased utilization (Chen et al., 2018; Hernandez et al., 2020; Mulcahy et al., 2018; Nabhan et al., 2018).

Biosimilars are often listed at a discounted price in comparison to reference biologics. Lower-price biosimilars can decrease the cost of treating patients and there is significant market pressure to reduce list prices for these drugs (Falit et al., 2015; Rompas et al., 2015). Researchers have estimated the potential cost savings from biosimilars would be $44.2 billion dollars between 2017 to 2026 (Mulcahy et al., 2018). However, in reality, there have been substantial barriers that have prevented a more widespread adoption of biosimilars than what was predicted (Chen et al., 2018; Crespi-Lofton and Skelton, 2017; Prasad et al., 2017; Zhai et al., 2019). These obstacles include gaps in acceptance and knowledge regarding biosimilars among patients and providers, and potential financial incentives for the payer for the coverage of reference biologics over biosimilars.

Research on the uptake of infliximab biosimilars shows an example of the impact financial incentives have on biosimilar uptake. Research has found that despite the availability of biosimilars for the reference biologic and the offering of these biosimilars at discounts of between 15% and 40% off the list price for the reference biologic (see Table 4), most major payers in the United States continue to name the reference biologic (infliximab) the preferred medication (Nabhan et al., 2018). In a published commentary by hospital system administrators regarding their experience with transitioning patients to a biosimilar (infliximab-dybb) for new infusions, they found the biggest obstacle to making the transition was third-party payer preference for the reference biologic over its biosimilar (Rossmann and Cross, 2020). While biosimilars are often listed at a discounted price in comparison to reference biologics, this third-party preference for a specific biologic has limited their uptake by enrollees (Rossmann and Cross, 2020). For enrollees who have a coinsurance for medications covered under the medical benefit, this means an enrollee could have higher cost sharing if they are being prescribed a reference biologic over a biosimilar.

Other factors have been suggested as barriers to utilization of biosimilars, such as the nocebo effect, wherein the lack of familiarity regarding biosimilars may lead to a patient to experience symptoms that are attributable to the patient's negative expectations regarding the unfamiliar drug. Thus, a patient would expect to have a negative outcome when he/she switches to a biosimilar from a reference biologic and

the symptoms are relieved once the patient is placed back on the reference biologic (Gonczi and Lakatos, 2019; Odinet et al., 2018; Pineles et al., 2018; Pouillon et al., 2018; Rossmann and Cross, 2020; Smeeding et al., 2019; Stebbing et al., 2020; Whalen, 2020).

Role of Pharmacy Benefit Managers

Insurance plans and policies may work with a pharmacy benefit manager (PBM) to manage drug benefits for their plans, which may include medications covered under the medical benefit. There are other third-party companies that plans and policies may contract with to provide medical necessity review. For medications covered under the pharmacy benefit, coverage is typically determined by a formulary set by the plan with the help of the PBM. The PBM is typically the entity involved with negotiating the prices of the drugs that will be covered with the manufacturer. Manufacturers may provide substantial discounts in the form of a rebate when their drug is chosen to be on the formulary. For medications covered under the medical benefit, PBMs may be involved with the creation of the list of covered medication, performing medical necessity and utilization management review, and billing. However, not all plans use all services provided by a PBM for medications covered under the medical benefit and may only use a PBM or another third-party entity to perform medical necessity and utilization management review. For medications covered under either the pharmacy or medical benefit even if the PBM was able to negotiate a lower drug price for the plan, the enrollee may not reap any of this discount because coinsurance paid by the enrollee for a medication is calculated based on the list price of the drug (Dolan, 2018; Karaca-Mandic et al., 2019; Mulcahy et al., 2018; Wahlster et al., 2015; Zhai et al., 2019).

Manufacturers' rebates can play a significant role in controlling costs for health plans and insurers. However, there is debate about whether these rebates are stifling the uptake of biosimilars (Falit et al., 2015; Hakim and Ross, 2017). Some biosimilar manufacturers argue that the rebates and exclusive agreements are anticompetitive and prevent new biosimilars from being added to a health plan or insurer's list of covered drugs, even if the cost of the biosimilar is lower than the reference biologic. Researchers have also suggested manufacturers may engage in "rebate traps" when they threaten to withdraw their rebate if a biosimilar is placed in a preferred position on a formulary (Yazdany, 2020). With rebates in place, the reference biologic may end up being cheaper than the biosimilar for the plan, thus there can be a financial benefit to having the biologic as the preferred drug (H Kim et al., 2020; Yazdany, 2020; Yazdany et al., 2018). As mentioned earlier, some biosimilar manufacturers have fought back legally arguing that rebates and exclusive agreements are anticompetitive and prevent new biosimilars from being used.[24,25]

Per CHBRP'S technical expert[26] if a PBM is used for medications covered under the medical benefit, it may require biologics and biosimilar medications be managed and distributed by a specialty pharmacy, particularly if the PBM is responsible for billing. For hospital-based clinics and treatment centers, this requirement may mean that orders of medications and shipment arrivals of these medications are off-site and logistical costs may be involved in ensuring that the medications make it to the infusion clinic or office in time for the infusion.

Utilization Management Techniques

Health plans and insurers use a wide range of utilization management strategies to manage the cost or safety of prescription medications. These may include prior authorization; step therapy protocols; age, quantity, or gender limits; copayments/coinsurance; preferred medication lists, and prescription medication tiers (which increase enrollee contributions for more costly prescription medications classified

[24] U.S. District Court. PFIZER INC. v. JOHNSON & JOHNSON and Janssen Biotech Inc. (17-cv-4180), Antitrust Litigation, District Court E.D. Pennsylvania; 2018.
[25] U.S. District Court. ROCHESTER DRUG COOPERATIVE INC. v. JOHNSON & JOHNSON (2:18-cv-00303), Antitrust Litigation, District Court E.D. Pennsylvania; 2018b.
[26] Personal communication, Robert Mowers, PharmD BCPS, UC Davis, April 2020.

in higher tiers). Step therapy and prior authorization policies vary between plans and insurers. As lists of covered medications are updated based on the introduction of new treatments and medical guidelines, these requirements are added to new medications as appropriate. Health plans and insurers analyze utilization patterns, clinical evidence, financial considerations, and government regulations and statutes to determine the type of care that requires these utilization management techniques.

This section describes step therapy and prior authorization, the utilization management techniques that SB 1452 addresses.

Step Therapy

Step therapy or "fail-first" protocols are one type of several utilization management protocols applied to prescription medications by health plans and insurers to control costs, ensure medication compatibility, and manage safety. They are also utilized as an enforcement tool for clinical recommendations and guidelines. Health plans/insurers use them to apply clinical guidelines established by professional societies and other recognized organizations, such as The National Quality Forum and the National Comprehensive Cancer Network, respectively. They require an enrollee to try and fail one or more alternate treatments prior to receiving coverage for the initially prescribed medication.

Step therapy protocols usually recommend starting with a medication that is less expensive and/or has more "post-marketing safety experience" (PBMI, 2015). They sometimes require starting with a less potent medication or dosage, perhaps with fewer side effects, and graduating to more potent medications as necessary (e.g., from prescription Motrin to OxyContin to treat pain). Some health plans/insurers require patients to try preferred brand-name medications after failing generic medications, prior to approving a nonpreferred medication that is prescribed by the provider. In the case of biologics, a patient may be required to try a nonbiologic medication prior to accessing coverage for an initially prescribed biologic or biosimilar medication. For example, consistent with recommendations by the American College of Radiology, a health plan or insurer may require an enrollee to "try and fail" with methotrexate, a generic small molecule medication, before covering the biologics Remicade or Rituxan under their medical benefit, or Enbrel or Humira under their pharmacy benefit. Generally, more expensive medications are covered when the patient fails to respond to the step therapy–required medication (PBMI, 2018). If coverage for the initially prescribed medication is declined under the step therapy, the prescriber may either reissue the prescription for the step therapy–required medication or appeal the decision directly to the health plan or insurer (requesting approval for a step therapy override). A patient always has the option to purchase the initially prescribed medication by paying the full cost out of pocket.

Prior Authorization

Prior authorization — also known as precertification, prior approval, or prospective review — is another utilization management technique. Like step therapy protocols, prior authorization protocols are used to enforce clinical guidelines from professional societies and organizations, and the FDA indication for use of specific medications. Pharmacy benefit managers and insurers/plans also use prior authorization as a safeguard to confirm that a patient's medications are compatible and have proven efficacy and safety (Allen and Ojong-Salako, 2015; AMCP, 2019).

In the context of biologics and biosimilars, prior authorization would require providers to establish eligibility and submit documentation demonstrating medical need to the plan/insurer for approval of coverage before a prescription is filled in order to qualify for payment. Health plans/insurers may also impose prior authorization requirements on nonpreferred medications in an effort to promote the use of preferred medications that they can procure at lower prices.

Disparities[27] and Social Determinants of Health[28] in the Use of Biologics and Biosimilars

Per statute, CHBRP includes discussion of disparities and social determinants of health (SDoH) as it relates to the use of biologics and biosimilars. Disparities are differences between groups that are modifiable.

Disparities

Disparities by age and race exist in patient access to, and subsequent use of, reference biologics and biosimilars. These disparities are dependent on the reference biologic or biosimilar in question. In addition to the studies described below that examined the U.S. reference biologics and biosimilars market, disparities in age and race were also found in studies of various reference biologics and biosimilars in European markets, which have a significantly greater number of these products available to patients (Farrukh and Mayberry, 2015; Putrik et al., 2016).

Age

CHBRP found studies demonstrating that older patients are less likely to have access to and initialize use of reference biologics or biosimilars. Jin and colleagues (2017) observed that older patients have a decreased chance of initiating disease-modifying antirheumatic drugs (DMARDs) for rheumatoid arthritis. With a 10-year increase in age, the odds of starting a biologic DMARD was reduced by 13% in patients with early untreated rheumatoid arthritis, and reduced by 29% in those with prevalent rheumatoid arthritis (Jin et al., 2017). Kim and colleagues (2015) analyzed Texas Medicaid prescription and medical claims database and found for patients 18 to 63 years of age with rheumatoid arthritis, patients were 1.6% less likely to start a biologic DMARD for each year increase in age (Kim et al., 2015). Age disparities are also found in the use of other biologics. A study by Reeder-Hayes et al. showed older patients have less access to Herceptin (trastuzumab), a reference biologic commonly used to treat breast cancer (Reeder-Hayes et al., 2016). Approximately one half of patients 65 years of age and older with stage I to III human epidermal growth factor receptor 2 (HER2)-positive breast cancer do not receive trastuzumab (Reeder-Hayes et al., 2016).

Race/ethnicity

CHBRP found one study that concluded black women with breast cancer are 25% less likely to receive the appropriate biologic within one year of diagnosis than white women (Reeder-Hayes et al., 2016). Similar disparities have been found in the patient population with rheumatoid arthritis. Jin and colleagues (2017) found that black patients with early untreated and prevalent rheumatoid arthritis were 40% and 30%, respectively, less likely to initiate a biologic DMARD compared to white patients (Jin et al., 2017). Another study analyzed rheumatoid arthritis therapies for patients in the Ethnic Minority Rheumatoid Arthritis Consortium and the Veteran Affairs Rheumatoid Arthritis Registry and found that nonwhite patients with rheumatoid arthritis were less likely to use biologics than white patients (Kerr et al., 2017).

[27] Several competing definitions of “health disparities” exist. CHBRP relies on the following definition: Health disparity is defined as the differences, whether unjust or not, in health status or outcomes within a population (Wyatt et al., 2016).

[28] CHBRP defines social determinants of health as conditions in which people are born, grow, live, work, learn, and age. These social determinants of health (economic factors, social factors, education, physical environment) are shaped by the distribution of money, power, and resources and impacted by policy (adapted from: CDC, 2014; Healthy People 2020, 2019). See CHBRP’s SDoH white paper for further information: http://chbrp.com/analysis_methodology/public_health_impact_analysis.php.

Social Determinants of Health (SDoH)

SDoH include factors outside of the traditional medical care system that influence health status and health outcomes (e.g., income, education, geography, etc.). CHBRP found no studies related to SDoH for patient access to biologics and biosimilars in California or the United States. However, studies conducted in Europe demonstrate that education and geography have significant impacts on access to these medications. Two studies found that urban residents in Central and Eastern European countries have greater access to biologics and biosimilars than those in rural areas (Codreanu et al., 2018; Rencz et al., 2015). Another showed less educated patients with rheumatoid arthritis have disadvantages accessing biologic DMARDs (Putrik et al., 2016).

Societal Impact of Patient Access to Biologics and Biosimilars in California

Patient access to, and subsequent use of, biologics and biosimilars creates a societal impact. In dollar terms, the societal impact can be indirect (lost wages, etc.), as well as direct (medical care, etc.). CHBRP is unable to find data that displays the larger societal impact of the ability for patients to access biologics and biosimilars specifically.

MEDICAL EFFECTIVENESS

As discussed in the *Policy Context* section, SB 1452 would prohibit DMHC-regulated health plans and CDI-regulated policies that provide coverage for reference biologics or the respective biosimilars under the medical benefit from limiting which reference biologic or its respective biosimilars are to be used when medically necessary. This provision is specific to physician- or clinician-administered reference biologics or their respective biosimilars. SB 1452 also prohibits prior authorization and step therapy in the decision to use a particular reference biologic or its respective biosimilar. Additional information on reference biologics and their biosimilars is included in the *Background on Biologics, Biosimilars, and Utilization Management Techniques* section. The *Medical Effectiveness* section of this report summarizes findings from evidence[29] on the safety of these reference biologics and their biosimilars and the impact of prior authorization and step therapy on reference biologic/biosimilar utilization and health outcomes.

Research Approach and Methods

Studies about the safety of physician- and clinician-administered biosimilars and the effect of prior authorization and step therapy requirements for these biosimilars on utilization and health outcomes were identified through searches of PubMed, the Cochrane Library, Web of Science, Embase, and Scopus. Websites maintained by the following organizations that produce and/or index meta-analyses and systematic reviews were also searched: the Agency for Healthcare Research and Quality (AHRQ), the International Network of Agencies for Health Technology Assessment (INAHTA), the National Health Service (NHS) Centre for Reviews and Dissemination, the National Institute for Health and Clinical Excellence (NICE), PubMed Health, the World Health Organization (WHO), and the Scottish Intercollegiate Guideline Network (SIGN).

The search was limited to abstracts of studies published in English.

The search was limited to studies published from 2015 to present, as 2015 was the year that the first biosimilar was approved by the FDA. The literature review returned abstracts for 177 articles, of which 14 were reviewed for inclusion in this report and 10 were included in this report. One of these 14 articles provided commentary on two separate randomized controlled trials; the reviewers excluded the commentary article and included two separate studies that reported about each trial individually. An additional 15 articles were reviewed for inclusion after being identified by an expert in rheumatology or through a literature search for another section of this report, 7 of which were included. A total of 19 studies were included in the medical effectiveness review for SB 1452. The other articles were eliminated because they did not focus on reference biologics and their biosimilars covered under the medical benefit, studied the efficacy of particular reference biologics or biosimilars, or studied the effects of reference biologics or biosimilars on out of pocket spending or cost-effectiveness. A more thorough description of the methods used to conduct the medical effectiveness review and the process used to grade the evidence for each outcome measure is presented in Appendix B.

CHBRP excluded studies of biologics or biosimilars that health plans and policies typically cover under the pharmacy benefit. These include the reference biologic Enbrel (etanercept) and its biosimilars Erelzi (etanercertp-szzs) and Eticovo (etanercept-ykro) as well as the reference biologic Humira (adalimumab) and its biosimilars Amjevita (adalimumab-atto), Cyltezo (adalimumab-adbm), Hyrimoz(adalimumab-adaz), Hadlima (adalimumab-bwwd), and Abrilada (adalimumab-afzb). Studies of these medications were excluded because SB 1452 only applies to reference biologics and biosimilars covered under the medical benefit.

[29] Much of the discussion in this section is focused on reviews of available literature. However, as noted in the section on Implementing the Hierarchy of Evidence on page 11 of the Medical Effectiveness Analysis and Research Approach document (posted at http://chbrp.com/analysis_methodology/medical_effectiveness_analysis.php), in the absence of fully applicable to the analysis peer-reviewed literature on well-designed randomized controlled trials (RCTs), CHBRP's hierarchy of evidence allows for the inclusion of other evidence.

The conclusions below are based on the best available evidence from peer-reviewed and grey literature.[30] Unpublished studies are not reviewed because the results of such studies, if they exist, cannot be obtained within the 60-day timeframe for CHBRP reports.

Key Questions

CHBRP's Medical Effectiveness review for SB 1452 addressed four key questions:

1. Are FDA-approved biosimilars as safe as their reference biologics?

2. Do prior authorization or step therapy requirements affect the utilization of biosimilars among patients who are treated with either physician- or clinician-administered reference biologics or their biosimilars?

3. Do prior authorization or step therapy requirements affect health outcomes among patients who are treated with either physician- or clinician-administered reference biologics or their biosimilars?

Methodological Considerations

The literature search conducted for this analysis did not yield many articles about the impact of prior authorization and step therapy for clinician-administered reference biologics on the utilization of reference biologics and their biosimilars or on health outcomes. In the case of reference biologics and their biosimilars for rheumatic diseases and inflammatory conditions, findings for medications administered by clinicians are sometimes combined with findings for self-administered medications, which limits generalizability to SB 1452, because the bill only affects coverage for clinician-administered medications. Few studies assessed reference biologics with biosimilars that treat cancer or the side effects of chemotherapy.

Outcomes Assessed

CHBRP assessed the safety of physician- and clinician-administered biosimilars compared to their reference biologics and the effect of prior authorization and step therapy requirements on utilization of these reference biologics and biosimilars and health outcomes.

Study Findings

This following section summarizes CHBRP's findings regarding the strength of evidence of the safety of physician- and clinician-administered biosimilars that are covered under the medical benefit and the effect of prior authorization and step therapy requirements on utilization of physician- and clinician-administered reference biologics/biosimilars and health outcomes. Each section is accompanied by a corresponding figure. The title of the figure indicates the test, treatment, or service for which evidence is summarized. The statement in the box above the figure presents CHBRP's conclusion regarding the strength of evidence about the effect of a particular test, treatment, or service based on a specific relevant outcome and the number of studies on which CHBRP's conclusion is based. Definitions of CHBRP's grading scale terms is included in the box below, and more information is included in Appendix B.

[30] Grey literature consists of material that is not published commercially or indexed systematically in bibliographic databases. For more information on CHBRP's use of grey literature, visit http://chbrp.com/analysis_methodology/medical_effectiveness_analysis.php.

The following terms are used to characterize the body of evidence regarding an outcome:

Clear and convincing evidence indicates that there are multiple studies of a treatment and that the large majority of studies are of high quality and consistently find that the treatment is either effective or not effective.

Preponderance of evidence indicates that the majority of the studies reviewed are consistent in their findings that treatment is either effective or not effective.

Limited evidence indicates that the studies have limited generalizability to the population of interest and/or the studies have a fatal flaw in research design or implementation.

Inconclusive evidence indicates that although some studies included in the medical effectiveness review find that a treatment is effective, a similar number of studies of equal quality suggest the treatment is not effective.

Insufficient evidence indicates that there is not enough evidence available to know whether or not a treatment is effective, either because there are too few studies of the treatment or because the available studies are not of high quality. It does not indicate that a treatment is not effective.

More information is available in Appendix B.

Findings Regarding the Safety of Biosimilars

Eleven studies examined the safety of biosimilars, most of which focus on the reference biologic infliximab and its biosimilars. Six of these studies assessed the safety of infliximab biosimilars among either patients not previously treated with a reference biologic or biosimilar or a mixed population of previously treated and untreated patients (Chingcuanco et al., 2016; Kim et al., 2017; HA Kim et al., 2020; Moots et al., 2018; Nakagawa et al., 2019; Scavone et al., 2018). Five of these studies assessed safety of biosimilars among patients who switched from a physician- or clinician-administered reference biologic to one of its biosimilars. Biosimilars studied included infliximab biosimilars, filgrastim biosimilars, trastuzumab biosimilars, and rituximab biosimilars (Barbier et al., 2020; Cohen et al., 2018; Jorgensen et al., 2017; Sieczkowska et al., 2016; Tony et al., 2019).

Glossary of Safety Indicators

Adverse Event (AE): "an unexpected medical problem that happens during treatment with a drug or other therapy" (Health, 2020) that does not necessarily indicate a causal link between the adverse event and the treatment (Ciavarra, 2014).

Adverse Drug Reaction (ADR): "a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or the modification of physiological function" (Rabinovitz et al., 2001) and indicates that a provider at least suspects that there is a causal relationship between the adverse reaction and the treatment (Ciavarra, 2014).

Suspect Drug: a drug associated with the ADR as determined by the initial reporter (Administration, 1992).

Studies assessing safety of biosimilars among patients who never had and/or had been previously treated with a reference biologic/biosimilar

Two systematic reviews assessed the safety of tumor necrosis factor (TNF) inhibitor biosimilars, which include biosimilars of the reference biologic infliximab (Remicade). One of these reviews (Moots et al., 2018) identified one study that showed that the occurrence of serious adverse events (AEs) was similar in the group that received the reference biologic infliximab (Remicade) and the group that received the biosimilar SB2, which is sold under the name infliximab-abda/Renflexis in the United States (Moots et al., 2018). Another systematic review found that, among 13 studies that compared several biosimilars to their

reference biologic (including studies that compared reference biologic infliximab [Remicade] to its biosimilars CT-P13 [sold in the United States as infliximab-dyyb/Inflectra], SB2, and BOW015) found that most studies reported similar proportions of patients with serious AEs as well as treatment-emergent AEs in the group that received the reference biologic and the group that received the biosimilar. Furthermore, no differences in the type of AEs were noted (Chingcuanco et al., 2016).

Four additional studies of CT-P13 (sold in the United States as infliximab-dyyb/Inflectra), a biosimilar for infliximab (Remicade), were published after the studies included in the systematic review (Kim et al., 2017; HA Kim et al., 2020; Scavone et al. 2018; Nakagawa et al., 2019). Kim et al. (2017) reported preliminary results from a randomized, double-blind, controlled phase 3 trial across 16 countries with a patient population of 220 individuals diagnosed with Crohn's disease. The authors found that after 6 weeks of treatment that the group of patients who received biosimilar CT-P13 had similar proportions of patients with at least one AE, at least one serious AE, and infusion-related reactions and infections compared to the group of patients who received the reference biologic infliximab (Remicade).

A retrospective study (Scavone et al., 2018) assessed the utilization patterns and safety profiles of reference biologic infliximab (Remicade) and its biosimilar CT-P13 (sold in the United States as infliximab-dyyb/Inflectra) in Italy, and found that 7.1% of adverse drug reactions (ADRs) were considered preventable. Additionally, adjusted analyses showed that the biosimilar CT-P13 (infliximab-dyyb/Inflectra) had a reduced probability of being reported as a suspect drug in safety reports regarding infection as opposed to other types of ADRs when compared to the reference biologic infliximab (Remicade) and that biosimilar CT-P13 (infliximab-dyyb/Inflectra) had an increased probability of being reported as a suspect drug in safety reports regarding infusion reactions as opposed to other types of ADRs compared to the reference biologic infliximab (Remicade).

Two prospective studies (HA Kim et al., 2020; Nakagawa et al., 2019) assessed the safety of CT-P13 (sold in the United States as infliximab-dyyb/Inflectra), a biosimilar for reference biologic infliximab (Remicade), by reporting the number of ADRs and AEs. Nakagawa et al. (2019) found that the incidence of ADRs among Japanese patients with inflammatory bowel disease who were treated with biosimilar CT-P13 and had never received reference biologic infliximab (Remicade) before was similar to the incidence of ADRs among Japanese patients with inflammatory bowel disease treated with reference biologic infliximab (Remicade). HA Kim et al. (2020), found that among 244 Korean patients treated with biologic CT-P13 there were a total of four severe AEs spread out over four types of AEs. None of the AEs were life-threatening, disabling, or associated with death.

Studies assessing safety of biosimilars among patients who switched from reference biologics

One systematic review (Barbier et al., 2020) identified 178 studies where outcomes of switching from a reference biologic to its biosimilar were reported for a variety of reference biologics, including five that are relevant to SB 1452: epotin afla (Epogen/Procrit) (five RCTs), filgrastim (Neupogen) (three RCTs, two retrospective studies), infliximab (Remicade) (nine RCTs, 91 real-world studies), rituximab (Rituxan) (five biosimilar development studies, two real-world studies), and trastuzumab (Herceptin) (one RCT). Another systematic review (Cohen et al., 2018) identified 90 studies that evaluated the possibility that switching from a reference biologic to its biosimilar could alter clinical outcomes among seven medications, including reference biologic filgrastim (Neupogen) and reference biologic infliximab (Remicade). Eight studies were included in both Barbier et al. and Cohen et al.'s systematic reviews. One study published after the studies included in Barbier et al. and Cohen et al.'s systematic reviews assessed the safety of the biosimilar GP2013 (Rixathon/Riximyo) compared to its reference biologic rituximab (Rituxan) (Tony et al., 2019).

Safety of reference biologic trastuzumab biosimilars

Barbier et al. (2020) identified a single study that assessed the reference biologic trastuzumab (Herceptin) with its biosimilar, which found that the safety of the reference biologic and its biosimlilar were similar.

Safety of reference biologic filgrastim biosimilars

Barbier et al. (2020) found that none of the identified studies comparing the reference biologic filgrastim (Neupogen) and its biosimilars indicated safety issues related to switching.

Cohen et al. (2018) found that among three studies conducted with healthy volunteers that examined the reference biologic filgrastim (Neupogen), all studies indicated that the safety profiles of reference biologic filgrastim (Neupogen) and its biosimilars were similar. Of the three multiple switch studies identified, one compared reference biologic filgrastim (Neupogen) to a biosimilar among 158 breast cancer patients. The study incorporated five switchover events and found no differences in overall safety over the course of the study.

Safety of reference biologic rituximab biosimilars

Barbier et al.'s systematic review also found that none of the identified studies comparing the reference biologic rituximab (Rituxan) and its biosimilars indicated safety issues related to switching (Barbier et al., 2020).

One study published after the studies included in Barbier et al.'s systematic review (Tony et al., 2019) reported the results of a multinational, randomized controlled trial conducted in the United States, Germany, Hungary, and Poland that included 107 patients diagnosed with rheumatoid arthritis who had previously received the reference biologic rituximab (Rituxan) for any length of time and compared the results of a group who continued to take reference biologic rituximab (Rituxan) to a group who switched to its biosimilar GP2013 (Rixathon/Riximyo). The FDA has not approved GP2013 (Rixathon/Riximyo) for use in the United States, but findings may be generalizable to the two biosimilars of rituximab (Rituxan) that the FDA has approved (rituximab-abbs/Truxima and rituximab-pvvr/Ruxience). The authors found no clinically meaningful differences in the rate of AEs observed between patients who continued to receive the reference biologic rituximab (Rituxan) and patients who switched to its biosimilar GP2013 (Rixathon/Riximyo).

Safety of reference biologic infliximab biosimilars

Cohen et al. (2018) identified one phase I and one phase III trial that found no clinically meaningful differences between the safety of the biosimilar CT-P13 (infliximab-dyyb/Inflectra) and its reference biologic infliximab (Remicade) in patients with ankylosing spondylitis or rheumatoid arthritis. Another phase III trial did not detect any changes in safety when comparing biosimilar SB2 (infliximab-abda/Renflexis) to its reference biologic infliximab (Remicade) in patients with moderate-to-severe rheumatoid arthritis. The authors included results from another study that concluded that safety parameters and reported outcomes for reference biologic infliximab (Remicade) and its biosimilar CT-P13 (infliximab-dyyb/Inflectra) were similar (Sieczkowska et al., 2016), although the study made no direct comparisons between people who received the two medications. Cohen et al.'s systematic review also included the NOR-SWITCH trial (Jorgensen et al., 2017), a phase 4 trial with 52 weeks of follow-up that enrolled 482 Norwegians diagnosed with inflammatory bowel disease (Crohn's disease or ulcerative colitis), spondyloarthritis, rheumatoid arthritis, psoriatic arthritis, or chronic plaque psoriasis who were being treated with reference biologic infliximab (Remicade). Participants were randomized to either continue receiving reference biologic infliximab (Remicade) or switch to receiving its biosimilar CT-P13 (infliximab-dyyb/Inflectra). The authors found that the overall frequency of AEs between the reference biologic infliximab (Remicade) group and the biosimilar CT-P13 (infliximab-dyyb/Inflectra) group were similar (160 [70%] vs. 164 [68%], respectively) and that the frequency of serious AEs between both groups was also similar (24 [10%] vs. 21 [9%], respectively).

Barbier et al.'s systematic review found, among several of RCTs of reference biologic infliximab (Remicade), that switching between the reference biologic (Remicade) and its biosimilars did not negatively affect safety outcomes (Barbier et al., 2020). Some real-world studies of the reference biologic infliximab (Remicade) and its biosimilars that were included in the systematic review reported differences

in safety outcomes. Additionally, multiple studies reported that patients discontinued treatments even though results of laboratory tests had not changed. Barbier et al. (2020) concluded that these discontinuations were mainly driven by patients' self-reported worsening outcomes, which the authors of these studies primarily attributed to the nocebo effect, or the idea that negative expectations about the efficacy of a treatment can lead to negative consequences following drug exposure (Odinet et al., 2018).

CHBRP identified three studies that address the nocebo effect on outcomes from studies of biosimilars. One systematic review that assessed open-label and double-blinded studies concluded that higher discontinuation rates in infliximab biosimilar open-label studies compared to double-blind studies support the theory of the nocebo effect but that the evidence was insufficient to draw conclusions about its existence (Odinet et al., 2018). One additional study acknowledged the possibility that the nocebo effect may contribute to AEs, but that there were not enough well-designed trials to accurately confirm that the nocebo effect causes adverse events among patients receiving biosimilars (Fleischmann et al., 2020). The authors of another study concluded that findings from studies of biosimilars indicate that the nocebo effect may have played a role in biosimilar discontinuation and suggested strategies for mitigating the nocebo effect (Colloca and Barsky, 2020).

Figure 1. Safety of Biosimilars Compared to the Reference Biologic

Summary of findings regarding safety of biosimilars compared to the reference biologics: There is limited evidence that that biosimilars are as safe as the reference biologics product based on 11 studies. Six studies that examined the safety of infliximab biosimilars among mixed populations of people who were previously treated with the reference biologic or were not previously treated concluded that the safety of infliximab biosimilars is similar to the reference biologic infliximab (Remicade) and one study that examined the safety of biosimilar GP2013 (Rixathon/Rixivo) concluded that the safety of GP2013 (Rixathon/Riximyo) is similar to its reference biologic rituximab (Rituxan) (note: GP2013 is not approved by the FDA). Five studies that assessed safety of biosimilars among patients who switched from reference biologics demonstrated that the groups continuing to take the reference biologic and the groups that switched to biosimilars had similar health outcomes. In addition, none of the studies assess biosimilars for reference biologic bevacizumab (Avastin), one of the medications for which SB 1452 would affect coverage, and only one study assessed biosimilars for the reference biologic trastuzumab (Herceptin).

Findings Regarding Impact of Prior Authorization and Step Therapy

Five studies assessed the impact of prior authorization (Binder-Finnema et al., 2019; Ozzello and Palestine, 2015; Palestine et al., 2016) and step therapy (Boytsov et al., 2020; Kozma et al., 2015) on reference biologic/biosimilar utilization or health outcomes.

Prior authorization

CHBRP did not identify any studies that directly addressed the impact of prior authorization on utilization of the reference biologics or their biosimilars for which SB 1452 would affect coverage or on health outcomes for the conditions treated with these medications.

There is evidence from two studies that prior authorization may affect physician's choice of treatment for conditions for which treatment options include reference biologics and their biosimilars that are typically covered under the medical benefit. These studies evaluated whether and how concerns about prior

authorization affects physicians' recommendations for treatment of uveitis, a condition for which recommended treatments include three reference biologics that have biosimilars (Ozzello and Palestine, 2015; Palestine et al., 2016).

In one study, pediatric ophthalmologists were surveyed about their first and second choice treatment options for a hypothetical patient diagnosed with uveitis associated with juvenile idiopathic arthritis, then were asked about their choice of treatment options once more assuming that the patient's cost for all medications would be equal and that there would be no prior authorization issues. Treatment options included four types of medications: (1) local implants (dexamethasone and fluocinolone acetonide implants), (2) nonbiologic immunosuppressives (methotrexate, cyclosporine, and mycophenolate mofetil), (3) biologic immunosuppressive medications (reference biologic infliximab [Remicade], reference biologic adalimumab [Humira], and reference biologic rituximab [Rituxan]), and (4) other medications. The authors found that, among the 132 respondents, the assumption that cost would be equal and that there would be no prior authorization issues for the patient did not have a significant effect on the percentage of physicians who chose methotrexate as a first-line therapy and a reference biologic as a second-line therapy (Palestine et al., 2016).

The second study surveyed uveitis and retina specialists about first and second choice therapies for three hypothetical patients diagnosed with uveitic conditions, then were asked about their first and second choice therapies again under the assumption that the patient's cost for all medications would be equal and that there would be no prior authorization issues. Therapy options included: (1) local implants (dexamethasone and fluocinolone acetonide implants), (2) immunomodulators (methotrexate, cyclosporine, and mycophenolate mofetil), (3) biologics (reference biologic infliximab [Remicade], reference biologic adalimumab [Humira], and reference biologic rituximab [Rituxan]), and (4) other medications. The authors found that, among the 106 respondents, the assumption that cost would be equal and that there would be no prior authorization issues for the patient was associated with an increase in the percentage of uveitis specialists whose first choice of treatment for ocular Behçet disease was a reference biologic (Ozzello and Palestine, 2015).

A qualitative study assessed how concerns about insurance coverage affected patient willingness to follow physician recommendations about DMARDs, including biologic DMARDs. The study analyzed transcribed conversations between patients diagnosed with rheumatoid arthritis and their clinician, where they discussed medication choices during an appointment. Among the 156 visits analyzed, the authors found that patient-clinician deliberations about medication choices were not solely focused on medical necessity among patients whose health plans or policies required prior authorization for biologics or other medications used to treat rheumatoid arthritis. In other words, patient uncertainty that their insurance would cover certain medically necessary medications disrupted the usual way in which patients and clinicians would decide upon a treatment plan together (i.e., based solely on medical necessity) (Binder-Finnema et al., 2019).

Figure 2. Impact of Prior Authorization on Biologic/Biosimilar Utilization and Health Outcomes

Summary of findings regarding impact of prior authorization on biologic/biosimilar utilization and health outcomes: There is insufficient evidence that prior authorization affects utilization of reference biologics and their biosimilar or the health outcomes of people who use these medications. CHBRP did not identify any studies that directly addressed this topic. Findings from one of two studies of physicians' responses to hypothetical scenarios concluded that prior authorization requirements for reference biologics affected treatment recommendations. Another study found that prior authorization requirements affected the conversations that patients with rheumatoid arthritis, a condition frequently treated with reference biologics or their biosimilars, had with their physicians about treatment options.

Step therapy

CHBRP did not identify any studies that directly address the impact of step therapy on utilization of the reference biologics or their biosimilars for which SB 1452 would affect coverage or on health outcomes for the conditions treated with these medications. The studies summarized below assessed the impact of step therapy requirements on utilization and treatment effectiveness among multiple reference biologics — including some for which SB 1452 would affect coverage — but did not compare differences in utilization or health outcomes between reference biologics and their biosimilars.

One retrospective cohort study assessed whether a step therapy policy for reference biologics affected utilization among patients diagnosed with a variety of conditions, including rheumatoid arthritis or inflammatory bowel disease. The clinician-administered biologics studied included reference biologic abatacept (Orencia), reference biologic infliximab (Remicade), reference biologic rituximab (Rituxan), and reference biologic tocilizumab (Actemra). The self-administered biologics studied included reference biologic dalimumab (Humira), reference biologic anakinra (Kineret), reference biologic certolizumab pegol (Cimzia), reference biologic etanercept (Enbrel), and reference biologic golimumab (Simponi/Simponi Aria). The study examined the percentage of patients with claims for clinician- and self-administered biologics by analyzing three separate cohorts; the first examined patients in step therapy plans versus all other patients in the database (population cohort), the second examined patients in step therapy plans versus patients that were members of plans that were roughly matched (matched cohort), and the third examined a subsample of patients that were members of step therapy plans that had sufficient data for a pre/post analysis (pre/post cohort). In the population cohort, 5.1% fewer patients had claims for clinician-administered reference biologics among step therapy plans compared to the overall plans (25.9% vs. 31.0%; $p<0.0001$). In the matched cohort, 7% more patients had claims for clinician-administered reference biologics among step therapy plans compared to matched plans (25.9% vs. 18.9%; $p<0.0001$). In the pre/post cohort, 2.8% more patients had claims for clinician-administered reference biologics among step therapy plans compared to pre/post plans (12.4% vs. 15.2%), although this result was not statistically significant ($p=0.0522$) (Kozma et al., 2015).

One retrospective study assessed treatment effectiveness of self-administered biologic DMARDs among patients with rheumatoid arthritis and psoriatic arthritis with and without prior authorization and step therapy requirements using a composite measure of treatment effectiveness. The DMARD a patient received at the start of the study period (i.e., the index medication) was deemed effective if the patient: (1) filled prescriptions for the medication for ≥80% of the time over a 12-month follow-up period; (2) did not switch to a new biologic DMARD or targeted synthetic DMARD; (3) did not have a new conventional synthetic DMARD added to their medication regimen; (4) did not have an increase in dose or frequency of their index medication; (5) had fewer than two intra-articular glucocorticoid medications after the third month of the follow-up period; and (6) had no more than 30 days of an oral glucocorticoid after the third month of the follow-up period or an increase of 120% or less in the dose of a prescription for an oral glucocorticoid. The authors found that patients with rheumatoid arthritis had 19% lower odds of treatment effectiveness if their plan had step therapy requirements and patients with psoriatic arthritis had 27% lower odds of treatment effectiveness if their plan had step therapy requirements compared to rheumatoid arthritis and psoriatic arthritis patients with plans that did not require step therapy (Boytsov et al., 2020). A subcomponent of treatment effectiveness, medication adherence, was also measured by Boytsov et al. The authors found that the odds of medication adherence was 19% lower among rheumatoid arthritis patients and 29% lower among psoriatic arthritis patients in health plans with step therapy protocols than patients in plans without step therapy protocols. However, because the claims studied only included self-administered biologic DMARDs, these findings may not be generalizable to the clinician-administered biologic DMARDs for which SB 1452 affects coverage because these medications are administered by a clinician.

Figure 3. Impact of Step Therapy on Biologic/Biosimilar Utilization and Health Outcomes

Summary of findings regarding impact of step therapy on biologic/biosimilar utilization and health outcomes: There is insufficient evidence that step therapy affects utilization of reference biologics and their biosimilar or the health outcomes of people who use these medications. CHBRP did not identify any studies that directly addressed this topic. CHBRP identified two studies of step therapy for reference biologics, including two reference biologics that are typically covered under the medical benefit and have biosimilars. One study found that step therapy requirements lowered the odds of treatment effectiveness among people who used self-administered biologic DMARDs, and another study had mixed results and found that one cohort of patients with step therapy plans had fewer claims for clinician-administered biologics but that two other cohorts of patients with step therapy plans had more claims for clinician-administered biologics compared to all patients. A limitation of this literature is that the studies examined different outcomes.

Summary of Findings

The medical effectiveness review concluded that there is limited evidence that physician- and clinician-administered biosimilars are as safe as their reference biologics. Across the 11 articles included in this section of the analysis, six of them studied the safety of biosimilars for the reference biologic infliximab (Remicade) among mixed populations of people who were previously treated with a biologic or were not previously treated, and five studied the safety of biosimilars among patients who switched from the reference biologics to the biosimilars. Most of these studies assessed the safety of infliximab biosimilars (most notably CT-P13, or infliximab-dyyb/Inflectra), but other studied biosimilars included filgrastim biosimilars, trastuzumab biosimilars, and rituximab biosimilars. The studies consistently found that rates of AEs were similar between patients treated with clinician-administered biologics and biosimilars. However, only one of these studies assessed biosimilars for trastuzumab (Herceptin) and none addressed biosimilars for bevacizumab (Avastin).

The medical effectiveness review also concluded that there is insufficient evidence that prior authorization and step therapy affect the utilization of physician- and clinician-administered reference biologics and their biosimilars or health outcomes of people treated with these medications. CHBRP did not identify any studies that directly addressed this topic. A few studies address prior authorization or step therapy for reference biologics but they do not examine the impact of these policies on utilization of biosimilars of these reference biologics or on health outcomes.

BENEFIT COVERAGE, UTILIZATION, AND COST IMPACTS

In this section, CHBRP provides an overview of baseline compliance with SB 1452 based on CHBRP's survey of health insurance plans and policies and a short discussion regarding the potential cost impacts of the bill. CHBRP does not provide any quantitative estimates of impact because CHBRP's data sources — Milliman's 2017 Consolidated Health Cost Guidelines Sources Database (CHSD) and 2017 MarketScan® Commercial Claims and Encounters Database (Marketscan) — do not include data on any of the biosimilars that entered the market after 2017. As shown in Table 1 in the *Background on Biologics, Biosimilars, and Utilization Management Techniques* section, the vast majority of biosimilars subject to this bill (FDA-approved biosimilars for Avastin, Epogen/Procit, Herceptin, Neluasta, Neupogen, Remicade, and Rituxan) were not yet on the market for use by 2017.

As discussed in the *Policy Context* section, SB 1452 would prohibit DMHC-regulated health plans and CDI-regulated policies that provide coverage for reference biologics or the respective biosimilars under the medical benefit from limiting which reference biologic or its respective biosimilars are to be used when medically necessary. This provision is specific to physician- or clinician-administered reference biologics or its respective biosimilars. SB 1452 also prohibits prior authorization and step therapy in the decision to use a particular reference biologic or its respective biosimilars.

Baseline Coverage

Currently, 100% of the 21,719,000 enrollees in commercial, Medi-Cal managed care, and CalPERS DMHC-regulated plans and CDI-regulated policies have health insurance that would be subject to SB 1452.

Current coverage of FDA-approved biosimilars and their associated reference biologics covered under the medical benefit was determined by CHBRP's survey of the largest (by enrollment) providers of health insurance in California. Responses to this survey represent 61.1% of all enrollees with health insurance subject to state mandates; broken down by market, responses to the survey represent 73.3% commercial enrollees, 100% of CalPERS enrollees, and 39.9% of Medi-Cal managed care enrollees. CHBRP queried health plans and policies on their coverage of reference biologics and biosimilars, prior authorization, and step therapy practices for reference biologic/biosimilar medication management.

Based on CHBRP's carrier survey, about 68% of enrollees enrolled in commercial plans and policies, 89% of enrollees in CalPERS plans, and 0% of enrollees in Medi-Cal managed care plans have coverage that is fully compliant with SB 1452 at baseline (Table 2). Full compliance was defined as being compliant for all of the following three provisions: (1) coverage of all physician- or clinician-administered biosimilars and their associated reference biologic[31], (2) no prior authorization for the covered reference biologic and its biosimilars related to medication choice, and (3) no step therapy for the covered reference biologic and its biosimilars related to medication choice. Under SB 1452, plans and policies could still have prior authorization and step therapy requirements for medical necessity as long as the requirement was applied equally to all covered reference biologics and their biosimilars.

Postmandate, 100% of enrollees would have coverage fully compliant with SB 1452.

Prior Authorization and Step Therapy

Table 2 shows the share of enrollees with health insurance compliant with SB 1452 at baseline based on responses to CHBRP's carrier survey. Medi-Cal managed care plans have greater coverage for the reference biologics and biosimilars (86% of enrollees in such plans have compliant coverage based on

[31] As discussed in the Policy Context section, plans and policies are not required to cover all biologics and biosimilars, but if at least one reference biologic or the biosimilar is covered, all medications within that specific medication line need to be covered in order to be compliant.

coverage of the medications) compared to enrollees in commercial or CalPERS plans and policies. However, coverage for the majority of enrollees in Medi-Cal managed care plans includes prior authorization (14% of Medi-Cal managed care plans reported no prior authorization) to access certain medications. 100% of Medi-Cal managed care plans reported there was no step therapy required for the covered reference biologics and their biosimilars. Enrollees in commercial plans and policies have the lowest levels of coverage (71%) for all reference biologics and their biosimilars, but the majority of enrollees were in plans and policies that have no prior authorization requirements (86%) to access certain medications that are covered. Most enrollees in CalPERS plans have coverage with no prior authorization to access certain medications (96% compliance) and only a share of enrollees have coverage that was noncompliant based on coverage of medications and step therapy. Table 3 shows compliance by reference biologic and its biosimilars.

As mentioned above, while SB 1452 prohibits prior authorization and step therapy in the decision to use a particular reference biologic or its biosimilar over another, SB 1452 does not prohibit prior authorization or step therapy related to medical necessity or clinical appropriateness of a medication. Most carriers surveyed by CHBRP responded that the plan or policy requires prior authorization for medical necessity for the reference biologics and biosimilars that would be subject to this bill (results not shown in table).

Table 2. Share of Enrollees with Health Insurance Compliant with SB 1452 at Baseline

	Commercial Market		CalPERS		Medi-Cal Managed Care Plans		Total	
	Percent	No. of Enrollees	Percent	No. of Enrollees	Percent	No. of Enrollees	Percent	No. of Enrollees
Coverage fully compliant with SB 1452	67.6%	8,678,000	71.8%	375,000	0%	-	41.7%	9,053,000
Coverage for reference biosimilars and their associated reference biologic (a)	71.0%	9,121,000	71.8%	375,000	85.6%	7,155,000	76.7%	16,651,000
No prior authorization for covered reference biologics & biosimilars (b)	90.1%	11,570,000	95.8%	500,000	14.4%	1,201,000	61.1%	13,272,000
No step therapy for covered reference biologics & biosimilars (c)	78.0%	10,018,000	90.6%	473,000	100%	8,356,000	86.8%	18,847,000

Source: California Health Benefits Review Program, 2020.

Notes: (a) Coverage for all biologics and biosimilars is defined as coverage of all biosimilars for each associated reference biologic.
(b) Prior authorization is specific to prior authorization requirements for specific medications, not related to medical necessity.
(c) Step therapy is specific to requirements to use specific medications, not related to medical necessity.

Among the health plans and policies that responded to questions about timeliness of prior authorization and step therapy requests, most noted that decisions about urgent requests are made within 24 to 72 hours and non-urgent requests within five days.

Table 3. Share of Enrollees with Health Insurance Compliant with SB 1452 by Reference Biologic and Their Respective Biosimilars at Baseline

	Commercial Market	CalPERS	Medi-Cal Managed Care Plans	Total
% of enrollees with coverage fully compliant with SB 1452: Avastin (bevacizumab) and its biosimilars	90.1%	86.5%	49.3%	74.3%
% of enrollees with coverage for bevacizumab and its biosimilars	100.0%	95.8%	100.0%	99.9%
% of enrollees with no prior authorization requirements for bevacizumab and its biosimilars	90.1%	95.8%	49.3%	74.5%
% of enrollees with no step therapy requirements for bevacizumab and its biosimilars	100.0%	90.6%	100.0%	99.8%
% of enrollees with coverage fully compliant with SB 1452: Epogen/Procrit (epoetin alfa) and its biosimilars	68.1%	71.8%	49.3%	61.0%
% of enrollees with coverage for epoetin alfa and its biosimilars	71.6%	81.2%	100.0%	82.7%
% of enrollees with no prior authorization requirements for epoetin alfa and its biosimilars	90.1%	95.8%	49.3%	74.5%
% of enrollees with no step therapy requirements for epoetin alfa and its biosimilars	78.0%	90.6%	100.0%	86.8%
% of enrollees with coverage fully compliant with SB 1452: Herceptin (trastuzamab) and its biosimilars	68.1%	86.5%	49.3%	61.3%
% of enrollees with coverage for trastuzamab and its biosimilars	71.6%	100.0%	100.0%	83.2%
% of enrollees with no prior authorization requirements for trastuzamab and its biosimilars	90.1%	95.8%	49.3%	74.5%
% of enrollees with no step therapy requirements for trastuzamab and its biosimilars	78.0%	90.6%	100.0%	86.8%
% of enrollees with coverage fully compliant with SB 1452: Neulasta (pegfilgrastim) and its biosimilars	67.6%	71.8%	0.0%	41.7%

	Commercial Market	CalPERS	Medi-Cal Managed Care Plans	Total
% of enrollees with coverage for pegfilgrastim and its biosimilars	71.0%	71.8%	85.6%	76.7%
% of enrollees with no prior authorization requirements for pegfilgrastim and its biosimilars	90.1%	95.8%	14.4%	61.1%
% of enrollees with no step therapy requirements for pegfilgrastim and its biosimilars	78.0%	90.6%	100.0%	86.8%
% of enrollees with coverage fully compliant with SB 1452: Neupogen (filgrastim) and its biosimilars	68.1%	71.8%	14.4%	47.5%
% of enrollees with coverage for filgrastim and its biosimilars	71.6%	71.8%	100.0%	82.5%
% of enrollees with no prior authorization requirements for filgrastim and its biosimilars	90.1%	95.8%	14.4%	61.1%
% of enrollees with no step therapy requirements for filgrastim and its biosimilars	78.0%	90.6%	100.0%	86.8%
% of enrollees with coverage fully compliant with SB 1452: Remicade (infliximab) and its biosimilars	68.1%	71.8%	49.3%	61.0%
% of enrollees with coverage for infliximab and its biosimilars	78.0%	85.4%	100.0%	86.6%
% of enrollees with no prior authorization requirements for infliximab and its biosimilars	90.1%	95.8%	49.3%	74.5%
% of enrollees with no step therapy requirements for infliximab and its biosimilars	78.0%	90.6%	100.0%	86.8%
% of enrollees with coverage fully compliant with SB 1452: Rituxan (rituximab) and its biosimilars	68.1%	71.8%	49.3%	61.0%
% of enrollees with coverage for rituximab and its biosimilars	78.0%	81.2%	100.0%	86.5%
% of enrollees with no prior authorization requirements for rituximab and its biosimilars	90.1%	95.8%	49.3%	74.5%
% of enrollees with no step therapy requirements for rituximab and its biosimilars	78.0%	90.6%	100.0%	86.8%

Source: California Health Benefits Review Program, 2020.
Notes: (a) Coverage for all biologics and biosimilars is defined as coverage of all biosimilars for each associated reference biologic.
(b) Prior authorization is specific to prior authorization requirements for specific medications, not related to medical necessity.
(c) Step therapy is specific to requirements to use specific medications, not related to medical necessity.

Baseline Utilization and Per-Unit Cost

As noted above, data on utilization of the majority of biosimilars to which SB 1452 would apply are not available within current claims data. Cost data are also limited to what is published and made available to the public. The list price or wholesale acquisition cost (WAC) of drugs are typically published by the manufacturer and made available to the public. These list prices are what the manufacturer sets as the undiscounted price to direct purchasers. However, list prices do not reflect any potential manufacturer discounts to payers (rebates) and other concessions that may contribute to lower net prices of drugs to the direct purchasers. There is a current lack of data available to researchers to examine net prices as data regarding discounts are not published.

Due to the nature of their manufacturing, biologics and biosimilars typically require refrigeration and other special handling and processing to ensure the products remain sterile; this contributes to the high costs of these specialty drugs. Table 4 shows the list prices for biologics and their respective biosimilars impacted by SB 1452. In contrast to small molecule generic medications (i.e., medications that contain the same chemical substance as a branded medication), which can be upwards of 80% less expensive than their brand-name counterparts, biosimilars are anywhere between 15% and 40% less expensive than their biologic counterparts.

Based on CHBRP's survey of health plans and policies, for reference biologics and their biosimilars covered under the medical benefit, some enrollees are required to contribute a coinsurance for the medication that was administered to them in office, along with a copay or coinsurance for the office visit. The medication coinsurance amount is calculated based on the list price of the medication. Some carriers indicated no coinsurance or copay was required for medications covered under the medical benefit.

Table 4. List Prices of Reference Biologics and Their Biosimilars Subject to SB 1452

Biologic & Corresponding Biosimilar	Unit	List Price/Wholesale Acquisition Cost (WAC)*
Avastin (bevacizumab) – reference biologic	400 mg	$3,079
Mvasi (bevacizumab-awwb)		$2,709
Zirabev (bevacizumab-bvzr)		$2,553
Procrit (epoetin alfa) – reference biologic	1000 Units	$25
Retacrit (epoetin alfa-epbx)		$11
Herceptin (trastuzumab) – reference biologic	420 mg	$4,249
Ogivri (trastuzumab-dkst)		$3,697
Herzuma (trastuzumab-pkrb)		$3,927
Trazimera (trastuzumab-qyyp)		$3,391
Kanjinti (trastuzumab-anns)		$3,697
Neluasta (pegfilgrastim) – reference biologic	6 mg	$6,231
Fulphila (pegfilgrastim-jmdb)		$4,175
Udenyca (pegfilgrastim-cbqv)		$4,175
Ziextenzo (pegfilgrastim-bmez)		$3,925
Neupogen (filgrastim) – reference biologic	480 mcg	$503

Biologic & Corresponding Biosimilar	Unit	List Price/Wholesale Acquisition Cost (WAC)*
Graniz (filgrastim-tbo)		$408
Zarxio (filgrastim-sndz)		$439
Nivestym (filgrastim-aafi)		$350
Remicade (infliximab) – reference biologic	100 mg	$1,160
Inflectra (infliximab-dyyb)		$942
Renflexis (infliximab-abda)		$751
Rituxan (rituximab) – reference biologic	100 mg	$940
Truxima (rituximab-abbs)		$845
Ruxience (rituximab-pvvr)		$717

Source: California Health Benefits Review Program, 2020. Based on American Journal of Managed Care Center for Biosimilars product press releases, cross checked with GoodRx drug price summaries for each product.

Note: *The WAC is the manufacturer's list price or undiscounted price to direct purchasers. This does not reflect any discounts that may be given to the purchasers; the purchasers can be payers, providers, distributors, or other entities.

Potential Postmandate Changes in Utilization and Cost

CHBRP lacks data to predict how SB 1452 would change utilization of biologics and biosimilars and subsequently impact expenditures and enrollee out-of-pocket expenses. Apart from the lack of data, CHBRP concludes that due to the high degree of uncertainty in how the various stakeholders (health plans and insurers, providers, enrollees) impacted by this bill would react, the overall impact of this bill on utilization and expenditures is unknown.

- Health plans and insurers: Current research suggests payer preference for reference biologics over biosimilars may have limited the uptake of biosimilars, stemming in part from arrangements made by PBMs to secure rebates and other concessions that reduce the cost of reference biologics for payers (See *Background on Biologics, Biosimilars, and Utilization Management Techniques* section for discussion) (Whalen, 2020; Yazdany, 2020; Zhai et al., 2019). With SB 1452, plans and policies would not be able to explicitly prefer a reference biologic or a particular biosimilar over another. However, it is possible plans and payers could limit incentives to use the most expensive biologic products in other ways. For example, Medicare pays for physician-administered biosimilars at the average sales price of the reference biologic plus 6% of the reference biologic's price as a way to incentivize physicians to utilize biosimilars (Burich, 2018). CHBRP is unable to determine how payers would likely respond to SB 1452.
- Providers: SB 1452 would give providers the ability to order and use products they deem preferable. While it is possible providers would shift towards preferring the lowest cost biosimilar for their patients, it is also possible providers would opt to use more expensive products that would be more profitable to their practices (Yazdany, 2020). CHBRP is unable to determine how providers would likely respond to SB 1452.
- Enrollees: SB 1452 could increase utilization of biosimilars by prohibiting preference of one reference biologic or its biosimilar over another by health plans and insurers. If an increased number of lower-cost biosimilars are utilized, enrollee cost sharing could be reduced given coinsurance calculations are based on list prices. Enrollees may prefer lower-cost biosimilars over more expensive reference biologics. However, should providers switch to prescribing the reference biologic over its biosimilar, cost sharing for enrollees could increase or remain the

same. The extent of this impact is unknown and CHBRP is unable to determine how enrollees would likely respond to SB 1452.

A discussion of various market pressures that may influence the use of reference biologics and biosimilars in practice is provided in the *Background on Biologics, Biosimilars, and Utilization Management Techniques* section.

PUBLIC HEALTH IMPACTS

As discussed in the *Policy Context* section, SB 1452 would prohibit DMHC-regulated health plans and CDI-regulated policies that provide coverage for reference biologics or the respective biosimilars under the medical benefit from limiting which reference biologic or its respective biosimilars are to be used when medically necessary. This provision is specific to physician- or clinician-administered reference biologics or its respective biosimilars. SB 1452 also prohibits prior authorization and step therapy in the decision to use a particular reference biologic or its respective biosimilar. The public health impact analysis includes estimated impacts in the short term (within 12 months of implementation) and in the long term (beyond the first 12 months postmandate).

Estimated Public Health Outcomes

Biologics and biosimilars treat a wide range of medical conditions and therefore the measurable health outcomes relevant to SB 1452 are dependent on both the treatment and condition in question. A significant change in utilization of these products could have an impact on the physical health outcomes of enrollees being treated by them. As presented in the *Medical Effectiveness* section, there is insufficient evidence based on a literature review that prior authorization and step therapy protocols affect utilization of biologics/biosimilars or health outcomes. CHBRP lacks data to predict utilization changes. Similarly, the response of payers, providers, and enrollees to SB 1452 is unknown (see *Benefit Coverage, Utilization, and Cost Impacts* section).

As noted above, SB 1452 prohibits health plans and insurers from using step therapy to require an enrollee from using a preferred drug. However, the bill does not prohibit the use of step therapy for medical necessity or clinical appropriateness. CHBRP found no studies examining the impacts of differing types of step therapy on health outcomes. While it is possible that the utilization of reference biologics and biosimilars that currently require step therapy protocols could increase postmandate, which may improve health outcomes for the conditions that they treat; however, many of the conditions for which reference biologics and biosimilars are prescribed are complex, chronic diseases that have limited existing treatments. Physicians may have few or no alternative treatments to choose from, or decide that a patient's current treatment will lead to a better prognosis. Therefore, CHBRP lacks data necessary to determine the public health outcomes from the removal of step therapy requirements under SB 1452.

SB 1452 also prohibits prior authorization that would require providers and patients to use one biologic or biosimilar over another. As a result, it is possible that the time required to access these medications could be reduced postmandate. However, health plans and insurers are still able to require prior authorization for medical necessity postmandate, therefore patients may still be required to wait a certain period of time for their medications. CHBRP found two studies demonstrating that prior authorization is associated with psychological and emotional distress for patients (Dickens and Pollock, 2017; Kelly et al., 2019), but the extent to which enrollees impacted by SB 1452 would experience this type of distress is unknown. No studies were found examining the impacts of different types of prior authorization on health outcomes. Accordingly, there is insufficient evidence to determine the impact of the removal of some prior authorization requirements on health outcomes by SB 1452 postmandate.

Due to the lack of data necessary to draw conclusions related to the health outcomes of SB 1452 postmandate, CHBRP is unable to determine the impact of the bill on the disparities discussed in the *Background on Biologics, Biosimilars, and Utilization Management Techniques* section regarding patient access to, and subsequent utilization of, biologics and biosimilars related to age and race.

In the first year postmandate, the public health impact of SB 1452 is unknown due to insufficient evidence regarding the impact of prior authorization and step therapy protocols on the utilization and cost of biologics or biosimilars. Thus, the impact of SB 1452 on disparities are also unknown. Please note that the absence of evidence is not “evidence of no effect.” It is possible that an impact — desirable or undesirable — could result, but current evidence is insufficient to inform an estimate.

LONG-TERM IMPACTS

In this section, CHBRP estimates the long-term impact of SB 1452, which CHBRP defines as impacts occurring beyond the first 12 months after implementation. Some interventions in proposed mandates provide immediate measurable impacts (e.g., maternity service coverage or acute care treatments), whereas other interventions may take years to make a measurable impact (e.g., coverage for tobacco cessation or vaccinations). These estimates are qualitative and based on the existing evidence available in the literature. CHBRP does not provide quantitative estimates of long-term impacts because of unknown improvements in clinical care, changes in prices, implementation of other complementary or conflicting policies, and other unexpected factors. When possible, CHBRP estimates the long-term effects (beyond 12 months postmandate) to the public's health that would be attributable to the mandate, including impacts on social determinants of health, premature death, and economic loss.

In the case of SB 1452, CHBRP lacks the data necessary to make conclusive statements on long-term impacts. This is due to insufficient evidence related to use and impact of prior authorization and step therapy for these drugs, and insufficient data related to their costs and utilization. It is also unknown how SB 1452 will influence future changes to the biologic and biosimilars market. Research efforts on biologics and biosimilars will likely continue for the foreseeable future considering their growing potential in the treatment of severe chronic diseases and the substantial revenue generated through their prescribed use. Recent federal efforts to reduce barriers to entry for new biosimilars on the market, such as the FDA's 2018 announcement to focus on anticompetitive practices, also signal a future increase in the utilization of these products (Dabrowska, 2019). With a greater number of biosimilars on the market, the costs of reference biologics and biosimilars are likely to decrease and stabilize over time. As new biosimilars enter the market, the number of reference biologics and biosimilars plans and policies would be required to cover would expand. The expanded availability may put pressure on payers and providers to increase access to, and utilization of, these lower-cost products. The ERISA Industry Committee recently published a report concluding that biosimilars present significant savings opportunities for large employers and their employees, indicating that some businesses and their beneficiaries are becoming increasingly aware of the availability of biosimilars and their potential financial impact in the prescription drug market (Socal et al., 2020). However, it is unknown how these changes may influence the impacts of SB 1452 in the long-term.

APPENDIX A TEXT OF BILL ANALYZED

On March 30, 2020, the California Senate Committee on Health requested that CHBRP analyze SB 1452. SB 1452 was amended on March 25, 2020 and April 17, 2020 and CHBRP has been asked to analyze the language as amended on April 17, 2020. The amended language is included below.

SENATE BILL NO. 1452

Amended March 25, 2020
Amended April 17, 2020

Introduced by Senator Morrell

February 21, 2020

An act to add Section 1342.715 to the Health and Safety Code, and to add Section 10123.1935 to the Insurance Code, relating to health care coverage.

LEGISLATIVE COUNSEL'S DIGEST

SB 1452, as amended, Morrell. Biological products.

Existing law, the Knox-Keene Health Care Service Plan Act of 1975, provides for the licensure and regulation of health care service plans by the Department of Managed Health Care, and makes a willful violation of the act a crime. Existing law also provides for the regulation of health insurers by the Insurance Commissioner. Existing law requires a health care service plan contract or a health insurance policy that provides coverage for outpatient prescription drugs to cover medically necessary prescription drugs, including nonformulary drugs determined to be medically necessary, and authorizes a health care service plan or health insurer to utilize formulary, prior authorization, step therapy, or other reasonable medical management practices in the provision of outpatient prescription drug coverage.

~~This bill would require a~~
With respect to a health care service plan contract or health insurance policy issued, amended, or renewed on or after January 1, 2021, ~~to include coverage for any biological product or biosimilar, as defined, if the health care service plan contract or health insurance policy provides for medical or prescription drug benefits and coverage for any biological product or biosimilar.~~ *that provides coverage for biological products or their respective biosimilars, as defined, this bill would prohibit a health care service plan or health insurer from determining which manufacturer's biological products or their respective biosimilars are to be used when medically necessary biological products or their respective biosimilars are prescribed.* The bill would prohibit a health care service plan or health insurer that is subject to this provision from ~~determining~~ *requiring prior authorization or step therapy to limit* which manufacturer's biological ~~product or biosimilar is to be a physician-administered biological product when a medically~~

~~necessary biological product or biosimilar is prescribed.~~ *products or their respective biosimilars are to be administered by a physician or clinician to an enrollee or insured.*

By imposing new requirements on a health care service plan, the willful violation of which is a crime, this bill would impose a state-mandated local program.

The California Constitution requires the state to reimburse local agencies and school districts for certain costs mandated by the state. Statutory provisions establish procedures for making that reimbursement.

This bill would provide that no reimbursement is required by this act for a specified reason.

DIGEST KEY
Vote: majority Appropriation: no Fiscal Committee: yes Local Program: yes

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BILL TEXT
THE PEOPLE OF THE STATE OF CALIFORNIA DO ENACT AS FOLLOWS:

SECTION 1. Section 1342.715 is added to the Health and Safety Code, immediately following Section 1342.71, to read:

1342.715.

(a) ~~A~~ *If a* health care service plan contract, including a specialized health care service plan contract, issued, amended, or renewed on or after January 1, 2021, ~~shall provide coverage for any biological product or biosimilar if that health care service plan contract provides for both of the following:~~ *provides coverage for biological products or their respective biosimilars as a medical benefit, that health care service plan shall not determine which manufacturer's biological products or their respective biosimilars are to be used when medically necessary biological products or their respective biosimilars are prescribed. This prohibition applies to physician- or clinician-administered biological products or their respective biosimilars.*

~~(1)Medical or prescription drug benefits.~~

~~(2)Coverage for any biological product or biosimilar.~~

(b) A health care service plan subject to this section shall not ~~determine which manufacturer's biological product or biosimilar is to be a physician-administered biological product when a medically necessary biological product or biosimilar is prescribed. This prohibition applies to any biological product or biosimilar covered under either an enrollee's outpatient prescription drug benefit or their medical benefit.~~ *require prior authorization or step therapy to limit which manufacturer's biological products or their respective biosimilars are to be administered by a physician or clinician to an enrollee.*

(c) For purposes of this section, the following definitions apply:

(1) "Biological ~~product"~~ *products"* has the same meaning as ~~that term is~~ *"biological product," as* defined under Section 262(i)(1) of Title 42 of the United States Code.

(2) ~~"Biosimilar"~~ *"Biosimilars"* has the same meaning as ~~that term is~~ *"biosimilar," as* defined under Section 262(i)(2) of Title 42 of the United States Code.

(3) ~~"Physician-administered biological product" means a biological product or biosimilar that is~~ *"Physician- or clinician-administered biological products or their respective biosimilars" means biological products or biosimilars that are* administered by a health care provider ~~in a provider's office,~~ *or clinician in a* hospital, clinic, *infusion center, their office,* or other health care facility setting.

SEC. 2.

Section 10123.1935 is added to the Insurance Code, immediately following Section 10123.1933, to read:

10123.1935.

(a) ~~A~~ *If a* health insurance policy, including a specialized health insurance policy, issued, amended, or renewed on or after January 1, 2021, ~~shall provide coverage for any biological product or biosimilar if that health insurance policy provides for both of the following:~~ *provides coverage for biological products or their respective biosimilars as a medical benefit, the health insurer shall not determine which manufacturer's biological products or their respective biosimilars are to be used when medically necessary biological products or their respective biosimilars are prescribed. This prohibition applies to physician- or clinician-administered biological products or their respective biosimilars.*

~~(1)Medical or prescription drug benefits.~~

~~(2)Coverage for any biological product or biosimilar.~~

(b) A health insurer subject to this section shall not ~~determine which manufacturer's biological product or biosimilar is to be a physician-administered biological product when a medically necessary biological product or biosimilar is prescribed. This prohibition applies to any biological product or biosimilar covered under either an insured's outpatient prescription drug benefit or their medical benefit.~~ *require prior authorization or step therapy to limit which manufacturer's biological products or their respective biosimilars are to be administered by a physician or clinician to an insured.*

(c) For purposes of this section, the following definitions apply:

(1) "Biological ~~product"~~ *products"* has the same meaning as ~~that term is~~ *"biological product," as* defined under Section 262(i)(1) of Title 42 of the United States Code.

(2) ~~"Biosimilar"~~ *"Biosimilars"* has the same meaning as ~~that term is~~ *"biosimilar," as* defined under Section 262(i)(2) of Title 42 of the United States Code.

(3) ~~"Physician-administered biological product" means a biological product or biosimilar that is~~ *"Physician- or clinician-administered biological products or their respective biosimilars" means biological products or biosimilars that are* administered by a health care provider ~~in a provider's office,~~ *or clinician in a* hospital, clinic, *infusion center, their office,* or other health care facility setting.

SEC. 3. No reimbursement is required by this act pursuant to Section 6 of Article XIII B of the California Constitution because the only costs that may be incurred by a local agency or school district will be incurred because this act creates a new crime or infraction, eliminates a crime or infraction, or changes the penalty for a crime or infraction, within the meaning of Section 17556 of the Government Code, or changes the definition of a crime within the meaning of Section 6 of Article XIII B of the California Constitution.

APPENDIX B LITERATURE REVIEW METHODS

This appendix describes methods used in the medical effectiveness literature review conducted for this report. A discussion of CHBRP's system for grading evidence, as well as lists of MeSH Terms, publication types, and keywords, follows.

Studies assessing the safety of physician- and clinician-administered biosimilars compared to their biologics and the effect of prior authorization and step therapy requirements on utilization of these biologics/biosimilars and health outcomes were identified through searches of PubMed, the Cochrane Library, Web of Science, Embase, and Scopus. Websites maintained by the following organizations were also searched: the Agency for Healthcare Research and Quality (AHRQ), the International Network of Agencies for Health Technology Assessment (INAHTA), the National Health Service (NHS) Centre for Reviews and Dissemination, the National Institute for Health and Clinical Excellence (NICE), PubMed Health, the World Health Organization (WHO), and the Scottish Intercollegiate Guideline Network (SIGN).

The search was limited to abstracts of studies published in English. The medical effectiveness search was limited to studies published from 2015 to present, as 2015 was the year that the first biosimilar was approved by the FDA. The literature regarding the safety of biosimilars consisted of a mix of study types. CHBRP did not identify any literature that directly addressed the impact of prior authorization or step therapy on biologic/biosimilar utilization and health outcomes.

Reviewers screened the title and abstract of each citation retrieved by the literature search to determine eligibility for inclusion. The reviewers acquired the full text of articles that were deemed eligible for inclusion in the review and reapplied the initial eligibility criteria.

The literature review returned abstracts for 177 articles, of which 14 were reviewed for inclusion in this report and 10 were included in this report. One of these 14 articles provided commentary on two separate randomized controlled trials; the reviewers excluded the commentary article and included two separate studies that reported about each trial individually. An additional 15 articles were reviewed for inclusion after being identified by an expert in rheumatology or through a literature search for another section of this report, 7 of which were included. A total of 19 studies were included in the medical effectiveness review for SB 1452.

Evidence Grading System

In making a "call" for each outcome measure, the medical effectiveness lead and the content expert consider the number of studies as well the strength of the evidence. Further information about the criteria CHBRP uses to evaluate evidence of medical effectiveness can be found in CHBRP's *Medical Effectiveness Analysis Research Approach*.[32] To grade the evidence for each outcome measured, the team uses a grading system that has the following categories:

- Research design;
- Statistical significance;
- Direction of effect;
- Size of effect; and
- Generalizability of findings.

The grading system also contains an overall conclusion that encompasses findings in these five domains. The conclusion is a statement that captures the strength and consistency of the evidence of an intervention's effect on an outcome. The following terms are used to characterize the body of evidence regarding an outcome:

[32] Available at: http://chbrp.com/analysis_methodology/medical_effectiveness_analysis.php.

- *Clear and convincing evidence;*
- *Preponderance of evidence;*
- *Limited evidence;*
- *Inconclusive evidence; and*
- *Insufficient evidence.*

A grade of *clear and convincing evidence* indicates that there are multiple studies of a treatment and that the large majority of studies are of high quality and consistently find that the treatment is either effective or not effective.

A grade of *preponderance of evidence* indicates that the majority of the studies reviewed are consistent in their findings that treatment is either effective or not effective.

A grade of *limited evidence* indicates that the studies had limited generalizability to the population of interest and/or the studies had a fatal flaw in research design or implementation.

A grade of *inconclusive evidence* indicates that although some studies included in the medical effectiveness review find that a treatment is effective, a similar number of studies of equal quality suggest the treatment is not effective.

A grade of *insufficient evidence* indicates that there is not enough evidence available to know whether or not a treatment is effective, either because there are too few studies of the treatment or because the available studies are not of high quality. It does not indicate that a treatment is not effective.

Search Terms (* indicates truncation of word stem)

Biologics/Biosimilars:

- Avastin
- Avsola
- Bevacizumab
- Bevacizumab-Awwb
- Bevacizumab-Bvzr
- Epoetin Alfa
- Epoetin Alfa-Epbx
- Epogen
- Filgrastim
- Filgrastim-Aafi
- Filgrastim-Sndz
- Fulphila
- Herceptin
- Herzuma
- Inflectra
- Infliximab
- Infliximab-Abda
- Infliximab-Axxq
- Infliximab-Dyyb
- Infliximab-Qbtx
- Ixifi
- Kanjinti
- Mvasi
- Neulasta
- Neupogen
- Nivestym
- Ogivri
- Ontruzant
- Pegfilgrastim
- Pegfilgrastim-Bmez
- Pegfilgrastim-Cbqv
- Pegfilgrastim-Jmdb
- Procrit
- Remicade
- Renflexis
- Retacrit
- Rituxan
- Rituximab
- Rituximab-Abbs
- Rituximab-Pvvr
- Ruxience
- Trastuzumab
- Trastuzumab-Anns
- Trastuzumab-Dkst
- Trastuzumab-Dttb
- Trastuzumab-Pkrb
- Trastuzumab-Qyyp
- Trazimera
- Truxima
- Udenyca

- Zarxio
- Ziextenzo

Zirabev

Topics:

- Adherence
- Age Factors
- Attitude to Health
- Biologics Utilization
- Coinsurance
- Complaints
- Continuation
- Copayment
- Cost of Illness
- Cost Sharing
- Deductible
- Discontinuation
- Disease-Modifying Antirheumatic Biologics
- Disparities
- Economic Loss
- Ethnicity
- Formularies
- Gender
- Health Care Outcome and Process Assessment
- Health Care Services
- Health Insurance Reimbursement
- Health Outcomes
- Health Services Accessibility
- Incidence
- Income
- Infusion Biologics
- Initiation
- Insurance
- Long Term Impacts
- Medication Adherence
- Morbidity
- Mortality
- Nocebo Effect
- Out-of-Pocket
- Pain Intensity
- Patient Compliance
- Payers
- Pharmacy and Therapeutics Committee
- Physician-Administered Biologics
- Physician-Administered Biosimilars
- Premature Death
- Prevalence
- Prior Authorization
- Productivity and Cost of Illness
- Quality of Life
- Race
- Remission
- Social Determinants of Health
- Socioeconomic Factors
- Step Edit
- Step Therapy
- Survival Rate
- Time to Initiation of Treatment
- Usage
- Utilization

APPENDIX C COST IMPACT ANALYSIS: DATA SOURCES, CAVEATS, AND ASSUMPTIONS

The cost analysis in this report was prepared by the members of the cost team, which consists of CHBRP task force members and contributors from the University of California, Los Angeles, and the University of California, Davis, as well as the contracted actuarial firm, Milliman, Inc.[33]

Information on the generally used data sources and estimation methods, as well as caveats and assumptions generally applicable to CHBRP's cost impacts analyses are available at CHBRP's website.[34]

Determining Public Demand for the Proposed Mandate

This subsection discusses public demand for the benefits SB 1452 would mandate. Considering the criteria specified by CHBRP's authorizing statute, CHBRP reviews public demand for benefits relevant to a proposed mandate in two ways. CHBRP:

- Considers the bargaining history of organized labor; and
- Compares the benefits provided by self-insured health plans or policies (which are not regulated by the DMHC or CDI and therefore not subject to state-level mandates) with the benefits that are provided by plans or policies that would be subject to the mandate.

On the basis of conversations with the largest collective bargaining agents in California, CHBRP concluded that unions currently do not include cost-sharing arrangements for description treatment or service. In general, unions negotiate for broader contract provisions such as coverage for dependents, premiums, deductibles, and broad coinsurance levels.

Among publicly funded self-insured health insurance policies, the preferred provider organization (PPO) plans offered by CalPERS currently have the largest number of enrollees. The CalPERS PPOs currently provide benefit coverage similar to what is available through group health insurance plans and policies that would be subject to the mandate.

To further investigate public demand, CHBRP used the bill-specific coverage survey to ask carriers who act as third-party administrators for (non-CalPERS) self-insured group health insurance programs whether the relevant benefit coverage differed from what is offered in group market plans or policies that would be subject to the mandate. The responses indicated that there were no substantive differences.

[33] CHBRP's authorizing statute, available at http://chbrp.com/CHBRP authorizing statute_2018_FINAL.pdf, requires that CHBRP use a certified actuary or "other person with relevant knowledge and expertise" to determine financial impact.
[34] See method documents posted at http://chbrp.com/analysis_methodology/cost_impact_analysis.php; in particular, see *2019 Cost Analyses: Data Sources, Caveats, and Assumptions*.

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A group of faculty, researchers, and staff complete the analysis that informs California Health Benefits Review Program (CHBRP) reports. The CHBRP **Faculty Task Force** comprises rotating senior faculty from University of California (UC) campuses. In addition to these representatives, there are other ongoing researchers and analysts who are **Task Force Contributors** to CHBRP from UC that conduct much of the analysis. The **CHBRP staff** coordinates the efforts of the Faculty Task Force, works with Task Force members in preparing parts of the analysis, and manages all external communications, including those with the California Legislature. As required by CHBRP's authorizing legislation, UC contracts with a certified actuary, **Milliman**, to assist in assessing the financial impact of each legislative proposal mandating or repealing a health insurance benefit.

The **National Advisory Council** provides expert reviews of draft analyses and offers general guidance on the program to CHBRP staff and the Faculty Task Force. CHBRP is grateful for the valuable assistance of its National Advisory Council. CHBRP assumes full responsibility for the report and the accuracy of its contents.

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CHBRP assumes full responsibility for the report and the accuracy of its contents. All CHBRP bill analyses and other publications are available at www.chbrp.org.

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