Research Protocol for Biosimilar Substitution Laws

Prepared by the Policy Surveillance Program Staff

October 2017
I. **Date of Protocol**: October 1, 2017

II. **Scope**: Compile state policies regulating pharmacist substitution of prescribed biological products (“biologics”) with biosimilars and its impact on pharmacist autonomy, patient’s rights and the role of the prescribing physician.

This longitudinal dataset includes coding questions meant to capture whether biosimilars can be substituted by pharmacists, the criteria for substitution, who must be notified of the substitution, the recordkeeping and labeling requirements related to substitution, and whether the law explicitly provides liability shields to pharmacists and prescribers for biosimilar substitution.

III. **Primary Data Collection**

a. **Project dates**: December 7, 2015 – October 1, 2017

b. **Dates covered in the dataset**: March 1, 2016 – October 1, 2017. This began as a cross-sectional dataset, capturing laws in effect as of March 1, 2016. An update was performed in October 2016 that collected laws effective March 1, 2016 and valid through October 1, 2016 to create a longitudinal dataset. This dataset most recently updated to include laws valid through October 1, 2017.

c. **Data Collection Methods**: The team building this dataset consisted of three legal researchers (“Researchers”) and one supervisor (“Supervisor”). The Researchers and the Supervisor were from the Policy Surveillance Program (PSP). The National Conference of State Legislatures (NCSL) website¹ and Westlaw Next were used to identify which states had legislation regulating pharmacist substitution of biosimilars. Secondary sources and a subject matter expert were also used to assist with defining the scope of the laws and regulations included in this dataset.

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d. **Databases Used**: Research was conducted using WestlawNext, NCSL and state-specific legislature websites.
   
i. Full text versions of the laws were collected from each respective state legislature website.
   
ii. Other sites such as Google, GoogleScholar, and HeinOnline provided additional secondary literature.

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e. **Search Terms**: “Biological Product”; “Biosimilar”, “Prescription Record”; “Interchangeable”
   
i. Key word searches were supplemented by examination of the table of contents of each relevant section of the state law identified for statues or regulations related to biosimilar substitution, recordkeeping and labeling requirements. Researchers also collected effective dates for the most recent version of relevant statutes and regulations.
   
ii. Once all the relevant statutes and regulations were identified for a jurisdiction, a master sheet was created that summarized the relevant statute or regulation, included the most recent statutory history for each statute and regulation, and added the effective date for that version of the law.
   
iii. All states with biosimilar substitution laws were 100% redundantly researched to confirm that all relevant law was being collected by the Researchers.

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f. **Initial Returns and Additional Inclusion or Exclusion Criteria**: Included laws pertaining to pharmacist substitution of biosimilars.
   
i. The following variables were researched while analyzing biosimilar substitution laws:
      
      - Criteria for substitution of biosimilars
      - Prescriber’s ability to prevent substitution
      - Notification to prescriber requirements
      - Notification to patient requirements
      - Recordkeeping requirements related to substitution
      - Labeling requirements related to substitution
      - Pharmacist and prescriber liability
      - Mandated cost consideration
   
   ii. Excluded laws pertaining specifically to:
      
      - General prescription substitution requirements not explicitly related to biosimilars
      - General pharmacy recordkeeping requirements not explicitly related to biosimilars
IV. Coding

a. Development of Coding Scheme: The Team worked in collaboration to determine the focus of the research and the key questions to be coded. The Researchers also conducted background research on the approval and use of biosimilars in the United States and extensively reviewed secondary sources on the topic. The Researchers conceptualized coding questions, then circulated them for review by the Supervisor. A subject matter expert provided additional feedback regarding the scope and content of the coding questions. When the questions were finalized, the Team entered the questions into the MonQcle.

i. Dataset terminology:

- “Biologic” is the FDA-licensed biological product originally prescribed by the physician.
- “Biosimilar” is the biological product approved by the FDA as biosimilar that is selected for substitution in place of the prescribed biological product.
- “Interchangeable” is the FDA designation indicating that a biosimilar is approved as interchangeable with another FDA-approved biological product.
- “Prescriber” is the prescribing physician.
- “Patient” is the individual for whom the prescription was written and is receiving the biological product. This may include an agent filling the prescription on the patient’s behalf.
- “Pharmacist” is the pharmacist or pharmacy intern dispensing the biological product.
- “Substitution” is the act of selecting and dispensing a biosimilar product for a prescribed biological product.
- “Right to refuse” is the patient’s right to demand the originally prescribed biological product instead of a substituted biosimilar.
- “Pharmacist provides information” includes a discussion required by law on a particular topic, e.g. cost of the biologic, how to use the biologic, expected responses, or a patient’s rights, in order for the pharmacist to make a substitution of a biosimilar for a biologic. It does not include a mandate that the patient be notified of the substitution.
- “Notification” is the required communication between a pharmacist and a prescriber, or between a pharmacist and patient, that a substitution of a biologic has been made by the pharmacist. This includes communication by making an entry into a shared medical records system that is accessible to the prescriber.
- “Recordkeeping requirements” are requirements for the pharmacist to keep prescription records of biosimilar substitutions.

b. General prescription labeling requirements not explicitly related to biosimilars.
• “Labeling requirements” are requirements related to the information on the label of the dispensed biosimilar.
• “Liability shield” is defined as protection for a pharmacist from legal responsibility for adverse events relating to a properly substituted biosimilar. If the liability shield is extended to the prescribing physician, the physician is protected from legal responsibility for pharmacist error relating to substitution of biosimilars.
• “State pharmacy board” is the board of pharmacy for each state that is responsible for regulating pharmacy practice in that state.

ii. Scope exclusion determinations:
• General prescription recordkeeping and labeling requirements not explicitly related to the substitution of biosimilars were not included unless specifically referenced or cross-referenced in the biosimilar substitution law.
• The method by which a prescriber indicated that substitution of the biologic by a pharmacist is not permitted was not included.
• Requirements regarding the method of communication that a substitution occurred by the pharmacist to the prescriber were not included.
• Labeling requirements related to the distributor or wholesale of a biological product were scoped out.
• Instances where state pharmacy law allows state pharmacy boards to permit waivers of any pharmacy requirements upon written request for good cause were scoped out.

b. Coding Rules:

i. The states coded in this dataset have laws pertaining to substitution by pharmacists of biosimilars for prescribed biologics.

ii. The legal text coded was limited to requirements relating specifically to the substitution of biosimilars. Statutes and regulations that are cited or cross-referenced that fell outside the scope of relevant policies, were not coded or included in the legal text.

iii. Below is explanation of individual coding questions and their respective responses.

• For the question, “Does the state regulate pharmacist substitution of biologics?”
  o States were coded as “yes” if they implemented legislation relating specifically to a pharmacist’s authority to substitute a biosimilar for a prescribed biologic.
  o States were coded “yes” if they amended their existing pharmacy substitution laws to include substitution of biological products.

• For the question, “Can pharmacists substitute a biosimilar for a biologic?”
  o This question was coded “yes” where the law either permitted or required pharmacists to substitute biosimilars for prescribed biological products given that certain criteria were met.
For the question, “Is substitution of a biosimilar required?”
  o This question was coded “yes” where the law required, rather than permitted, pharmacists to substitute biosimilars for prescribed biological products given that certain criteria were met.
  o “No” was coded when substitution was not required. For example, language that a pharmacist “may” substitute a biosimilar.
  o “No, unless the prescription was subsidized with public funds” was coded where substitution in required for prescriptions subsidized with public funds, e.g. Medicaid. This answer was only coded when this exemption was explicitly stated in the subsections relating to biosimilars.
  o A caution note was provided where there is a requirement that a pharmacist shall not substitute an interchangeable biological product if the patient requests the prescribed biological product.

For the question, “What criteria must be met in order to substitute a biosimilar?”
  o This question was coded where the law indicated certain criteria must be met before a pharmacist can choose to or is required to substitute a biosimilar.
  o “FDA designation as interchangeable biosimilar” was coded where the law limited substitution of biological products to biosimilars labeled as interchangeable by the FDA for the prescribed product.
    ▪ A caution note was provided if “interchangeable biosimilar” was also defined to include a “therapeutically equivalent” biological product.
  o “Biosimilar costs less than biologic” was coded where the law required the biosimilar selected for substitution to cost less than or equal to the prescribed biological product. A caution note was included where the cost must be less than or equal to the prescribed biologic.
  o “Prescriber does not expressly prohibit substitution” was coded for express prohibitions, including oral instructions, written instructions, or indications on a prescription form by the prescriber.
  o “Prescriber does not expressly prohibit substitution” was coded where the prescriber was required to indicate whether substitution was prohibited or permitted.
    ▪ For example, states where a prescriber must sign one of two signatures lines on a written prescription, with one permitting substitution and one requiring the biological product to be dispensed as written. See S.C. Code § 39-24-20(B).
  o “Patient requests biosimilar” was coded where patients are required to expressly ask for substitution to occur.
  o “Pharmacist provides information” was coded where the law required pharmacists to communicate certain information to the patient prior to or upon dispensing. This was not coded when the only information required to be provided by the pharmacist is that substitution occurred, as this was coded separately under patient notification. This answer choice was not selected for instances where the patient must provide affirmative consent.
  o “Affirmative consent by patient to substitution” was coded where the patient was required to expressly agree to substitution. In states where the patient had to be notified of their right to refuse, but no explicit consent was required, this response was not coded.
For an example, see Ohio Rev. Code §4729.38 Substitution of generically equivalent drug or interchangeable biological product; conditions, “(3) The pharmacist or the pharmacist's agent, assistant, or employee shall inform the patient or the patient's agent if a generically equivalent drug or interchangeable biological product is available at a lower or equal cost and of the person's right to refuse the drug selected.”

- “Prescriber indicates substitution is permissible” was coded where the pharmacist is prohibited from substitution unless the prescriber indicates on the prescription that substitution is permitted.
- Requirements related to prescriber or patient notification were not coded as substitution criteria and were coded under a separate question.
- Requirements for a biological product to be in stock were not coded.
- Substitution criteria outside the scope of this dataset were not coded.

For the question, “What information must a pharmacist provide to the patient when dispensing?”

- This question was coded where “Pharmacist provides information” was coded in the parent question.
- “Cost” was coded where the pharmacist must inform the patient that a lower or equal cost biosimilar is available when filling the prescription.
- “Use” was coded where the pharmacist was required to instruct patient on use and dosage of substituted biosimilar.
- “Expected responses” was coded where pharmacist was required to counsel patient on responses expected while using the substituted biosimilar.
- “Right to refuse” was coded where the pharmacist must instruct the patient that he or she has a right to refuse substitution of the biosimilar and to receive the prescribed biologic.
- “Right to refuse” was coded where the pharmacist must ask the patient to choose between the biosimilar and prescribed biologic.
- “No requirements to provide information explicitly stated in the law” was coded where “Pharmacist provides information” was not coded in the parent question.
- Provision of information outside the scope of this dataset were not coded.

For the question, “Can the prescriber prevent substitution of an interchangeable biosimilar for the biologic?”

- This question was coded “yes” where the law prohibited pharmacists from making a substitution if the prescriber communicated to the pharmacist that substitution should not occur.
- This question was coded “yes” where the prescriber instructed the pharmacist orally or by indicating or writing “dispense as written” or “brand medically necessary” on the prescription form.
- Requirements for the prescriber’s instructions to be in good faith or medical judgment were not captured.

For the question, “Does the prescriber need to be notified of the substitution?”

- This question was coded “yes” where the pharmacist is required to communicate to the prescribing physician that a substitution occurred or the name of the biosimilar that was dispensed.

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- Notification was satisfied by entry of the substitution into a shared medical records system that is accessible by the prescribing physician.

- For the question, “How soon must the prescriber be notified of substitution?”
  - States requiring prescriber notification within a reasonable amount of time were coded as the answer choice “specific timeframe not listed.”
  - All listed timeframes refer to business days and/or exclude weekends and holidays.

- For the question, “Are there exemptions from the prescriber notification requirement?”
  - This question was coded “yes” where the law provides explicit exemptions from the requirement for pharmacists to notify prescribers that a substitution has occurred.

- For the question, “What exemptions from the prescriber notification requirement are explicitly stated in the law?”
  - “Prescription refill” was coded where pharmacists are not required to notify prescribers of substitution when refilling an existing prescription.
  - This question was coded where substitutions occurring in certain settings were exempt from the requirement for pharmacists to notify prescribers of substitution, including nursing homes, hospitals, and other assisted living facilities.
    - “Nursing homes” was coded when there was an exemption for “nursing facilities.”
    - “Assisted living facility” was coded when there was an exemption for “hospice in-patient” facilities.

- For the question, “Must the patient be notified of substitution?”
  - This question was coded “yes” where pharmacists were required to inform the patient that a biosimilar substitution was made prior to, upon, or after dispensing a prescription.
  - Laws that include posting of signs informing patients about biosimilar substitution for biologics satisfy the notification requirement.
  - Laws that require pharmacists to notify the patient of the biosimilar substitution by noting the words “substituted for” on the prescription label satisfy the notification requirement.
  - Laws that require the patient to provide affirmative consent satisfy the notification requirement and were coded “yes.”

- For the question, “How many years must pharmacists keep records of the substitution?”
  - Specific time periods were coded when recordkeeping requirements explicitly stated the time frame in the relevant biosimilar statute or where pharmacy recordkeeping requirements were cross-referenced that explicitly stated the time frame.
  - “No specific timeframe listed in the law” was coded either when there was a recordkeeping requirement but the timeframe was not specified or when there was no explicit recordkeeping requirement.
• For the question, “What are the labeling requirements related to the substitution of biologics?”
  o This question was coded where prescription labeling requirements were explicitly related to the substitution of biosimilars.
  o This question was coded where prescription labeling requirements were cross-referenced in the relevant biosimilar statute.
  o “Name of biologic dispensed” was coded where the state explicitly required the label to contain the name of the biosimilar that was selected and dispensed.
  o “Name of the manufacturer” was coded where the state explicitly required the label to contain the name of the manufacturer of the biosimilar that was selected and dispensed.
  o “Indicate substitution occurred” was coded where there must be an explicit comment on the label that substitution of the prescribed biologic occurred.
  o “Name of the prescribed biologic” was coded where the state law explicitly required the label to contain the name of the biologic that was originally prescribed.
  o “Address of manufacturer” was coded where the state law explicitly required the label to contain the address of the manufacturer of the biosimilar that was selected and dispensed.
  o If labeling requirements did not explicitly apply to substitution of biosimilars, this question was coded as “no labeling requirements listed in law.”
  o Labeling requirements outside the scope of the dataset were coded as “no labeling requirements listed in the law.”

• For the question, “Does the law explicitly provide a liability shield for pharmacist substitution of a biologic?”
  o This question was coded “yes” where the law explicitly states that pharmacists are no more liable for the substitution of biosimilars than they would be for the substitution of generic drugs.
  o This question was also coded “yes” where the law states that a pharmacist is no more liable for dispensing an interchangeable biological product than they would be for dispensing the prescribed product.
  o “Responsibility” was coded the same as “liability” regarding pharmacist liability when substituting a biosimilar.

• For the question, “Does the liability shield for substitution of a biologic extend to the prescribing physician?”
  o This question was coded “yes” where the law explicitly states that prescribing physicians are not liable for biosimilar substitutions made by the pharmacist.

• For the question, “Must the state pharmacy board maintain a list of interchangeable biologics on their website?”
  o This question was coded “yes” where the law specified that the state pharmacy board is required to maintain a current list of FDA-approved interchangeable biosimilars on its public website.

V. Quality Control
a. **Quality Control – Background Research:** The Researchers independently recorded the relevant citations of every jurisdiction with a biosimilar law. The Supervisor reviewed this redundant research and the Team resolved each divergence prior to collecting the relevant laws.

b. **Quality Control – Coding:** Quality control consisted of the Supervisor exporting the data into Microsoft Excel to examine the data for any missing entries, citations, and caution notes. 100% of the jurisdictions that had a law were redundantly coded throughout the life of the project (33 of 51). The Supervisor assigned the first 15 jurisdictions for redundant coding and the rate of divergence was 2.6% on September 26, 2017. The Supervisor assigned the next 18 jurisdictions for redundant coding and the divergence rate was 2.85% on October 10, 2017. The Supervisor assigned the remaining records to be redundantly coded and the divergence rate spiked to 7% on October 23, 2017.

In order to assess the overall error rate of the dataset, Statistical Quality Control (SQC) was performed after all of the original and redundant coding was completed. Ten percent of the dataset’s coding questions were checked across all records. After stratifying the dataset to include only records for which a biosimilar law existed, 1440 coding instances could potentially be checked. Of those, a random sample of just below 10%, 130 records, was drawn.

This SQC yielded a divergence rate of 2.3%, with 3 divergences in total. The divergences were discussed and resolved by the Team.

c. **Quality Control – Final Check:** Prior to publication, the Supervisor downloaded all coding data into Microsoft Excel to do a final review of coding answers, statutory and regulatory citations, and caution notes. All unnecessary caution notes were deleted, and all necessary caution notes were edited for publication.