The Biosimilar Substitution Battle: Branded Biotech Wins in Virginia, North Dakota, and Utah

BY JOY LIU

Branded biotechnology firms and biosimilar companies have been battling over the issue of therapeutic substitution of biosimilars for some time. Biosimilar substitution is governed at a state level and refers to the practice whereby pharmacists may substitute a biosimilar product for the branded product prescribed by a physician. Both branded and biosimilar companies have been engaged in efforts to influence the outcome of pending state legislation. With the passage of the first state biosimilar substitution laws in late March and early April, round one of the battle appears to have been won by branded biotechnology firms.

New Biosimilar Substitution Laws

On March 21, 2013, Virginia became the first state in the nation to regulate dispensing of interchangeable biosimilar products when governor Bob McDonnell signed a bill into law concerning the substitution of biosimilars. This article analyzes the Virginia law, examines the principles set forth by the Biotechnology Industry Organization (“BIO”) on biosimilar substitution, and reviews biosimilar substitution legislation pending in most other states.

Under Virginia law, pharmacists are permitted to dispense a biosimilar in lieu of a prescribed biological product only if the biosimilar meets federal safety standards for interchangeability. A similar provision requires a substituted chemical drug to be “therapeutically equivalent” to the drug prescribed. Virginia law defines therapeutically equivalent drug products as those having the same active ingredient, strength or concentration, dosage form, and route of administration. The drugs must also be classified as “therapeutically equivalent” in the Food and Drug Administration’s “Orange Book.”

If the prescriber has specified “brand medically necessary” on the prescription or has given specific oral dispensing instructions, substitution of an interchangeable biosimilar for a prescribed biological product, or a therapeutically equivalent chemical drug for a prescribed drug, is not permitted. If the patient “insists” on receiving the prescribed biological product or chemical drug, substitution is likewise prohibited.

There are also other similarities between the Virginia biosimilar substitution provisions and small-molecule drug substitution provisions. In both cases, patients must be notified if a substitution has been made. The name of the manufacturer or distributor of the interchangeable biosimilar or generic drug—as well as the product name, in the case of an interchangeable biosimilar—must also be noted by the pharmacist in his or her records, as well as on the prescription label. Additionally, the words “generic for” and the name of the branded drug must follow the name of a substituted generic drug. The name of a substituted interchangeable drug must be followed by both the words “substituted for” and the name of the prescribed biological product.

Two key differences exist, however, between the new biosimilar substitution provisions in the Virginia law and current provisions regarding drug substitutions. First, if an interchangeable biosimilar is substituted by

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the pharmacist, the pharmacist or the designee of the pharmacist must notify the prescriber or the prescriber's staff—either electronically, in writing or by phone—within five business days or within a time frame established by a collaborative agreement between the pharmacist and the prescriber. Small-molecule drug substitution does not require such notice.

Second, when an interchangeable biosimilar is substituted by a pharmacist, the pharmacist or the designee of the pharmacist must provide retail cost information for both the prescribed product and the interchangeable biosimilar to the patient. In such instances, "retail cost" is defined as "the actual cost to be paid by a retail purchaser to a pharmacy for a drug at the prescribed dosage and amount." If a therapeutically equivalent chemical drug is substituted for a prescribed drug by a pharmacist, however, no notice to the patient is required. The pharmacist need only ensure that the dispensed drug product has a retail price lower than that of the drug prescribed. The provisions mandating prescriber notification and retail price notification to the patient will expire on July 1, 2015.

A week after Virginia passed its biosimilar legislation, North Dakota did as well. Like the Virginia law, the North Dakota law limits biosimilar substitution to interchangeable biosimilars, prohibits substitution if the prescriber has stated that the brand is medically necessary, and requires notification to the patient. The North Dakota law also requires notification to the physician of substitution but, unlike the Virginia law, which requires notice within 5 days, the North Dakota law requires notice within 24 hours of the substitution. Several days later, Utah also passed biosimilar substitution legislation substantively similar to the Virginia and North Dakota laws, but allowing 3 days for notice to be given to prescribers of substitutions. Neither the Utah nor the North Dakota laws includes a cost provision similar to the one in the Virginia law.

**BIO Perspective**

The Biotechnology Industry Organization ("BIO"), the trade organization representing branded biotechnology firms, strongly supports the two notice provisions described above, identifying them as critical safeguards that must govern the substitution of interchangeable biosimilars. BIO also advocates other safeguards, including a requirement that substitution only be permitted if FDA has designated a biosimilar as interchangeable with the prescribed biologic product. Meeting this standard would require a biosimilar product to be expected to produce a clinical result identical to that of the reference biologic product in any given patient. Additionally, if the product is administered more than once to an individual—as most biologics are—the risk in terms of safety or diminished efficacy from switching between the reference biologic product and the biosimilar cannot exceed the risk of using the reference biologic product without such switching.

BIO also advocates for substitution laws that permit the prescribing physician to prevent substitution by clear indication on the prescription. The rationale for this position is that prescribing physicians are best suited to evaluate treatment history and options for their patients, and those physicians should be allowed to dictate exactly which product they believe should be dispensed to their patients. This position mirrors many existing generic drug substitution laws, which allow the prescriber to mandate the prescribed product by writing "brand medically necessary" on the prescription itself.

BIO also advocates for laws enabling prescribing physicians to prevent substitution by clear indication on the prescription. The rationale for this position is as follows: prescribing physicians are in the best position to evaluate their patients' treatment history and options, and should therefore have the authority to dictate the medication they believe their patients should receive. Many state generic drug substitution laws already mirror this position by allowing prescribers to mandate the prescribed product on the prescription itself by writing "brand medically necessary."

BIO also supports laws requiring pharmacists to keep thorough records of biologic substitutions. Should a patient experience an adverse reaction, these records could prove invaluable in helping to determine whether the adverse reaction should be attributed to the prescribed or to the substituted product.

**GPhA Perspective**

In a press release issued on the day Virginia passed its biosimilar substitution law, the Generic Pharmaceutical Association ("GPhA") characterized the law as "well-intentioned" but carrying burdensome "red tape" that threatens the positive impact of biosimilars. GPhA believes that "the time to pass this legislation is after FDA guidance has been issued" and that legislation passed at this time "pre-empts" FDA. For this reason, GPhA urges state legislators to "reject biosimilar substitution legislation that preempts the FDA." The press release does not specify, however, what kind of guidance FDA should issue before it would be acceptable for states to pass biosimilar substitution laws, nor does it offer any specific biosimilar substitution guidelines or principles that GPhA supports.

Presumably, GPhA would prefer biosimilar substitution laws that are more similar to existing state substitution laws regarding generic drugs. For example, in most states, generic substitution laws do not require the pharmacist to give notice of the substitution to the prescriber, nor of cost information to the patient. In addition, in many states, a pharmacist is not only permitted to substitute a generic drug when the prescription is written for the branded drug, but is required to substitute if the generic is available to the patient at a lower cost. Thus, GPhA may take the position that if FDA has approved a biosimilar product as interchangeable with its reference product, pharmacists should be permitted to automatically substitute the interchangeable product for a prescribed branded product. Indeed, the biosimilar law itself states that "interchangeable products may be substituted for the reference product without the intervention of the prescribing healthcare provider."

**Legislation in Other States**

Automatic substitution of interchangeable biologics is not likely, however, to be in the cards, as evidenced by the fact that most countries in Europe, where biosimilars have been on the market for eight years, prohibit automatic substitution. Similarly, automatic substitution is not permitted under the Virginia law, nor is it contemplated in the legislation considered by most other states.
The legislation in those states is substantively very similar to the Virginia law and reflects many, if not all, of the points advocated for by BIO. The relevant states include Arkansas, California, Colorado, Florida, Illinois, Indiana, Oregon, Pennsylvania, and Texas.

Certain of the states have provided for an even higher standard for permitting substitution in their pending bills. In Indiana, the prescribing physician must affirmatively indicate on the prescription that the pharmacy “may substitute” a biosimilar. In the absence of this affirmative statement by the prescribing physician, the pharmacist may not substitute a biosimilar. This is different from the Virginia law because the presumption in Virginia is that substitution will occur unless the physician objects. In the Indiana proposal, the presumption is against substitution, unless the physician explicitly permits it. In Pennsylvania and Utah, the person presenting the prescription, i.e., the patient, must affirmatively consent to biosimilar substitution. In Pennsylvania, that consent must be in writing.

Massachusetts, however, has introduced House Bill 1927, which stands alone as the only biosimilars substitution bill that does not include all of BIO’s recommended biosimilar substitution safeguards. The Massachusetts bill requires only that a biosimilar be deemed interchangeable by FDA and that the prescribing physicians have the option to prevent substitution by instruction on a given prescription. No notice requirement, either to physicians or patients, is included in the bill, nor is there any specific requirement for recordkeeping.

Bills in Mississippi, Maryland, Arizona, and Washington have been rejected, but revised bills could be reintroduced later this year.

Impact of Biosimilar Substitution Laws

It remains to be seen whether the bills pending in these states will ultimately be passed into law and if so, whether the substance of those laws will follow Virginia’s lead. The impact of these laws, if passed, is also unclear. For example, although the laws may require pharmacists to notify prescribers of substitutions, and although this would be an additional step in the process and one that pharmacists have not dealt with before, the requirement may not be unduly burdensome. This is due to both the increasing use of e-prescribing and communication technology that could make it much easier for pharmacists to notify prescribers of substitutions. Similarly, giving notice of the cost differential between a prescribed product and a substituted product could be easily included on the computer-printed label for the prescription that typically already includes many other data points from the patient’s file (e.g., name, physician, name of drug, use instructions, insurance company).

Given the complexity of biological products and the fact that even interchangeable biosimilars will not be exact replicas of branded biologics, implementing these relatively minor notice provisions may be a low-cost method of ensuring the protection of the public health.