UCONN

AN ONGOING CE PROGRAM
of the University of Connecticut
School of Pharmacy

EDUCATIONAL OBJECTIVES

GOAL: To highlight the similarities and differences between traditional prescription drug products (or small molecules) and biologics, and discuss factors associated with the introduction of biosimilars.

After participating in this activity pharmacists will be able to:

- Discuss the major outcome and cost implications to healthcare pursuant to use of biologics
- Differentiate between innovator small molecules and biologics, classic generics, and biosimilars
- Describe the manufacturing processes used for biopharmaceuticals and their implications for making biosimilar products
- Discuss the clinical implications of biosimilars

After participating in this activity, pharmacy technicians will be able to:

- Discuss the principle behind biologics and biosimilars
- Describe differences between biologics and biosimilars with specific emphasis on naming conventions
- Identify proper storage temperatures for biologics and biosimilars
- Recognize when to refer patients who have concerns about cost of innovator products or switching to biosimilars to the pharmacist for recommendations

The University of Connecticut School of Pharmacy is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Pharmacists and pharmacy technicians are eligible to participate in this knowledge-based activity and will receive up to 0.2 CEU (2 contact hours) for completing the activity, passing the quiz with a grade of 70% or better, and completing an online evaluation. Statements of credit are available via the CPE Monitor online system and your participation will be recorded with CPE Monitor within 72 hours of submission

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To obtain CPE credit, visit the UConn Online CE Center **https://pharmacyce.uconn.edu/login.php** . Use your NABP E-profile ID and the **session code**

17YC95-AKX99 for pharmacists or
17YC95-YKZ62 for pharmacy technicians

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For questions concerning the online CPE activities, email joanne.nault@uconn.edu.

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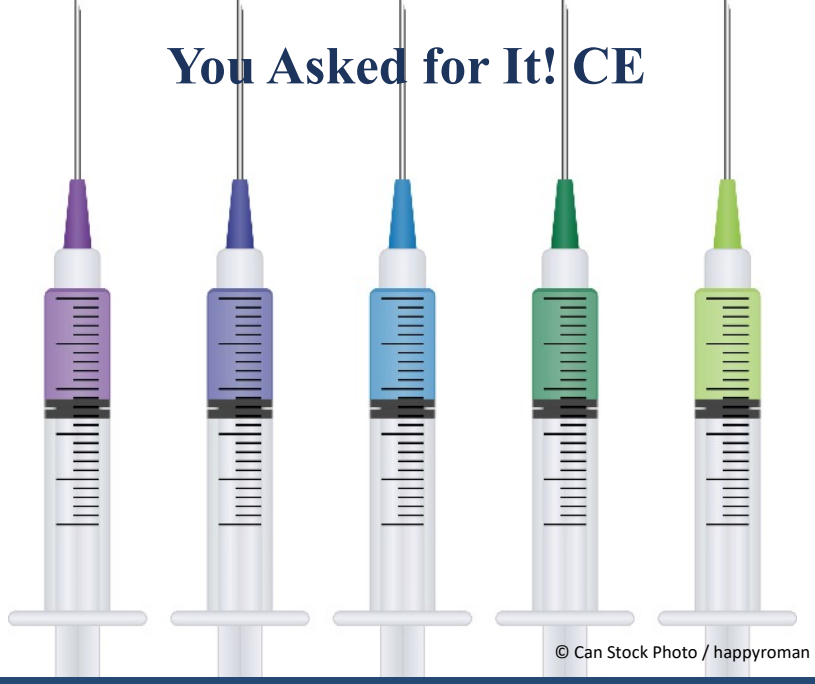

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Biosimilars: The 360º View

ABSTRACT: It wasn't until recently that the US Food and Drug Administration (FDA) gave manufacturers the ability to create biosimilars – biologic products similar to innovator products and expected to deliver the same clinical outcomes. In theory, biosimilars fill the same role that generic drugs do for small molecules. They are, however, significantly different in many ways. This article addresses the expected impact of biosimilars on prescription costs, laws associated with biosimilars, biologics that are currently on the market, those expected to arrive within the next few years, and the pharmacy team's role in recommending biosimilars in counseling patients who use them.

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DISCLOSURE OF DISCUSSIONS of OFF-LABEL and INVESTIGATIONAL DRUG USE: This activity may contain discussion of off label/unapproved use of drugs. The content in views presented in this educational program are those of the faculty and do not necessarily represent those of the University of Connecticut School of Pharmacy. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

INTRODUCTION

This article provides a 360º overview of biosimilar and interchangeable biological products as it:

- discusses the biologic drug revolution and its impact of the cost of drug therapy
- reviews drug laws pertaining to small molecules generic drugs and their impact on spending
- compares and contrasts small molecule and biological drugs and why there cannot be a generic biologic
- discusses drug laws pertaining to biologic drugs and the FDA's categories of biosimilar and interchangeable biological products
- identifies biosimilars currently on the market and those on the horizon, and
- concludes by focusing on the pharmacy team's role when biosimilars are available.

THE BIOLOGIC DRUG REVOLUTION

The science-fiction of yesterday is being used to create biologics—large complex molecules derived from living organisms—for diseases that were treated nonspecifically or even untreated in the past.[1] As the biologic complexities of these diseases are unraveled, the ability to specifically target diseases with medications that maximize the opportunity for benefits and minimize extraneous adverse effects is within our reach.[1] In important target diseases including inflammatory disorders, multiple sclerosis, and cancer, biologics have resulted in some advantages over traditional small molecule drugs (see sidebar). Benefits include quicker onset of benefit, efficacy in previously refractory patients, or a superior benefits to harm balance.[2,3,4] However, these advances use complex technology and processes and the resultant treatment's specificity limits the size of the market that can be targeted (**Table 1**).[5] Currently the most common biologic therapies impact only 0.2% of patients in commercial health plans, versus a prevalence of 12.1% for the most common small molecule drugs in three disease categories.[5]

Pause and Ponder:
What are the major differences between small molecule drugs and biosimilars? How can you best explain them to patients?

Sidebar: Biologics vs. Small Molecules

Biologics have large chemical structures (often a mix of related molecules) with high molecular weights, and often have complex three-dimensional structures. They are produced in living cell cultures using processes that are difficult to control, and the final product is usually less stable than small molecule products. It's difficult to characterize (draw) the structure of a biologic.

Small molecules are simple structures of low molecular weight, usually referred to as "drugs." They are produced using simple chemical processes, and it's easy to make identical, stable copies. Their structures are clear, and easy to draw.

Cost Impact of Biologic Drugs

As will be discussed, biological agents are much more difficult to produce, purify/refine, and store than small molecule drugs.[2-4] Coupled with such a low prevalence of use compared with small molecule drugs, the cost is comparatively much greater.[5] As illustrated in **Table 2**, the top three disease categories where biological drugs are predominantly used are markedly more expensive than in diseases dominated by small molecule drugs. In addition, the drug spending per prescription on inflammatory, oncology, and multiple sclerosis are anticipated to rise by 10% to 30% each year for the next three years as compared with slightly decreased spending per prescription for hypercholesterolemia, hypertension, and asthma over that same time period.[5] Another sector of the biologic market is comprised of orphan drugs, drugs that treat rare (fewer than 200,000 patients) or ultra-rare (fewer than 1,000 patients) diseases. Costs of orphan drugs are astronomical at approximately $118,820 per year. In addition, pharmaceutical manufacturers' return on investment is 1.14 times greater than for other types of drug development given tax breaks, smaller sample size requirements for clinical trials, and other incentives in the Orphan Drug Act of 1984.[6] This is why research and development (R&D) spending on orphan drugs now constitutes 23% of total R&D budgets and why prescription drug costs will continue to skyrocket as new rare disease treatments increasingly come to market.[6]

The category of specialty drugs, which are predominantly comprised of regular biologic and orphan biologic drugs, were responsible for 73% of overall prescription spending growth over the past 5-years.[7,8] Currently specialty drugs represent less than 1% of US prescriptions but 1/3 of prescription drug spending.[1] It is predicted that total spend on specialty drugs will grow from $138 billion in 2010 to $253 billion in 2020, an 83% increase that will have specialty drugs accounting for more than 50% of all medication spending.[1,9]

Table 1. Commercial Health Plan Utilization and Cost of Biologic and Small Molecule Drugs for Major Diseases.[5]

Biologic			Small Molecule		
Inflammation	Scripts/PMPY	0.03	**Hypercholesterolemia**	Scripts/PMPY	1.08
	Prevalence	0.40%		Prevalence	10.50%
	Cost/Script	$3588		Cost/Script	$36
Oncology	Scripts/PMPY	0.01	**Hypertension**	Scripts/PMPY	2.48
	Prevalence	0.10%		Prevalence	16.80%
	Cost/Script	$7891		Cost/Script	$14
Multiple Sclerosis	Scripts/PMPY	0.01	**Asthma**	Scripts/PMPY	0.41
	Prevalence	0.10%		Prevalence	$0.09
	Cost/Script	5056		Cost/Script	$69

PMPY = per member per year

Pause and Ponder:
How many of your patients use biologics? What are their concerns about using these agents?

Generic Small Molecule Drugs: Impact on Healthcare/Drug Spending

Before discussing opportunities for increased competition in the biologic market, it's important to discuss generic small molecule drugs and their impact on prices.

The Drug Price Competition and Patient Term Restoration Act of 1984 provided an abbreviated pathway for generic approval of small molecule drugs with bioequivalence (very similar bioavailability when given at the same dosage under similar conditions) based on achieving similar blood concentrations.[10] Small molecule drugs that have no known or suspected bioequivalence issues are designated with an "A" rating and those with sufficient *in vivo* and/or *in vitro* evidence to support bioequivalence are designated "AB" rated. These "AB" designated drugs are published in the FDA's "Orange Book" and are generally considered substitutable for a reference small molecule drug at the pharmacy without further consultation with the prescriber pursuant to intricacies of state pharmacy laws. Some states allow "A" designated drugs ("AA", "AN", "AO", "AP", and "AT") that are not "AB" designated to also be substituted based on pharmacist judgment; others prevent automatic generic substitution for select small molecule drugs even if they have an "AB" rating.[10,11] The Agency for Healthcare Research and Quality commissioned an assessment of the impact of using innovator vs. generic antiepileptic agents. They found that either would provide similar efficacy and safety when initiated *de novo*, but switching between them could induce short term medical instability with increase healthcare resource utilization.[12] As such, several states banned automatic generic substitution for antiepileptics and a select few states also prevent automatic generic substitution for other narrow therapeutic index drugs (warfarin, levothyroxine, and select immunomodulatory drugs) as well.[13]

The availability of lower cost generics and automatic generic substitution has resulted in more than $1.67 trillion in small molecule drug cost savings from 2007 to 2016.[14] Approximately 88% of traditional small molecule drugs are available as generic medications up from 50% in the 1990s. The large number of generics has helped hold drug spending on traditional pharmaceuticals; spending did not increase from 2014 to 2016.[5,8] It is important to understand that having a single generic only reduces prices nominally. Once three or more generics are available for an innovator drug, prices tend to fall 50% to 75%.[15]

BIOLOGICS ARE NOT SMALL MOLECULE DRUGS

The Drug Price Competition and Patient Term Restoration Act of 1984 cannot be applied to rather complex, genetically engineered biologics. Derived from living cells or tissues and often comprised of polysaccharides, proteins, or nucleic acids, they are not small molecule drugs.[16] Whereas aspirin is made up of 21 atoms, an IgG antibody biologic drug is comprised of more than 20,000 atoms. These large molecular weight products garner biologic activity from

- the number of atoms that comprise them
- the molecule's basic structure
- complex secondary or tertiary folding of the macromolecules in three dimensional space, and
- the existence and orientation of side groups that may be produced by one species but not another or even in one subspecies but not another.

Many biologics are monoclonal antibodies, enzymes, or hormones. Research scientists genetically engineer living organisms or tissues to produce the biologic. They cultivate the most effective cell lines and then place them in strictly controlled environments to minimize variability. The biologic drug is then harvested, isolated, and purified. These cell lines and other cell lines that are created from them are proprietary to the manufacturer (like a vineyard or a brewery having proprietary microorganism strains that give their product unique characteristics). The growth conditions the cells are exposed to are also owned by the manufacturer. Given the unique nature of biological drugs and their complexities, exact copies of biologic drugs cannot be created.[16]

BIOSIMILARS ARE NOT GENERICS

In the Biologics Price Competition and Innovation Act of 2009, an abbreviated pathway for biosimilar and interchangeable biological products were described. Biosimilars must have no clinically meaningful differences with the FDA-approved reference biologic product it was compared to in terms of safety, purity, and product potency.[17] Interchangeable biologic products

- are biosimilar to an FDA-approved reference product
- can be expected to produce the same clinical result as the reference product, and
- are associated with similar risk if patients alternate or switch between the biological and the reference product or use the reference product continuously.

The manufacturer's application for a biosimilar or interchangeable biological product must include: (1) analytical studies demonstrating that the biological product is "highly similar" to the reference product notwithstanding minor differences in clinically inactive components; (2) animal studies (including the assessment of toxicity); and (3) clinical data sufficient to demonstrate safety, purity, and potency in at least one indication for which the reference product is currently approved.[17] An application for an interchangeable biological product also must include data demonstrating the proposed interchangeable biological product is expected to produce the same clinical result as the reference product in any given patient. Unless the biologic agent is to be given only one time to treat or cure a disease, a proposed interchangeable agent needs data demonstrating that alternating between the innovator product and the interchangeable product is not greater than the risk of using one of the products without switching.[17] This addresses the issue demonstrated for generic antiepileptics which were equally safe or efficacious as their innovator products but created clinical instability when substituted.[12]

Biosimilar and interchangeable biologic products are given the name of the reference (innovator) product followed by a dash and a four letter suffix so the prescribers can prescribe it specifically, the pharmacy can identify an interchangeable biologic product for substitution, or surveillance programs can conduct pharmacovigilance efforts.[18] In rare circumstances when the innovator name with or without a suffix would be ambiguous and lead to medical errors, the FDA can also ascribe a prefix to the innovator name.[18]

The "Purple Book" is the biologic product equivalent of the "Orange Book" and contains lists of biological drugs produced by the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research.[19] It includes the date the FDA licensed a biological product, the exclusivity expiration date, and whether there are currently any FDA-approved biosimilars (designated "B") or interchangeable biologic products (designated "I"). The "B" designation for biosimilar should not be confused with a "B" rated generic small molecule drug in the "Orange Book" which have different definitions and connotations. The "Purple Book" is updated periodically with the latest update on September 14, 2017 and is available online (insert link).[19]

Biosimilars on the Market and the Horizon

To date, there are no interchangeable biologic products on the US market but **Table 2** contains reference biologic drugs that currently have FDA-approved biosimilars and a list of biosimilars that are under development.[19,20] This may not be a complete list of late stage biosimilars under development because pharmaceutical companies do not have to disclose if they are creating, testing or assessing a biosimilar.

According to the RAND Corporation, use of biosimilars and interchangeable biological products will save the US Healthcare System approximately $44 billion dollars by 2024.[21] This is only an estimated 4% of total biologic drug spending over that time period and the estimates are dependent on familiarity on the part of the health-care providers and patients about the importance of these alternatives to innovator products.[21]

In Europe, legislation launching biosimilars was approved much earlier than in the United States. There, the reductions in drug pricing has been modest with TNF-alpha biosimilars reducing the overall spending in that therapeutic class by 10%. They have seen reductions of up to 27% for red and white cell stimulating drugs.[22] These reductions in drug spending have also been associated with an interesting dynamic not seen in small molecule drugs: some innovators have reduced their prices to match that of biosimilar products. The complexity associated with the creation, isolation, and purification of the biosimilars means that the manufacturing costs are high and the differential price between the initial innovator's price and the biosimilar is slight. To protect market share, innovator manufacturers have been willing to reduce profitability to stave off competition. This may be due to the small target markets for biologic drugs versus small molecule drugs in the marketplace and the need to maintain market dominance to substantiate the maintenance of complex cell lines and manufacturing processes. This is also a disincentive to the introduction of multiple biosimilars for each innovator product; based on generic drug data, this is where the greatest reductions in price would result. A recent assessment found that the first biosimilar cornered the greatest amount of market share, approximately 3/4 of the biosimilar market, while the second and third biosimilars had very little penetration.[22] Overall, the US can only anticipate price reductions of about 15% to 20% when biosimilars are introduced, but this is still a substantial reduction in overall prescription drug spending.

The Pharmacists Role in Diseases Treated with Biosimilars

Pharmacists in managed care and specialty pharmacies play an important role in the treatment of patients with biologic agents and pharmacist's involvement in biosimilars could be equally important.[1]

Managed care pharmacists work on understanding disease states and developing or administering step therapy, formulary tiering, value-based purchasing agreements, and disease state management programs to maximize affordability of prescription drug coverage for their clients.[1]

Pharmacists in specialty pharmacies offer a range of services including distributing and selling products, educating patients about their biologic drugs, monitoring patients reactions to the medications, administering the drugs, and handling paperwork

Table 2. FDA Approved Biosimilars and Biosimilars Under Development.[19,20]			
Reference Name	**Biosimilar name**	**Year Biosimilar Approved**	**Therapeutic Action/USe**
FDA APPROVED			
Filgrastim (Neupogen)	Filgrastim-sndz (Zarxio)	3/6/2015	Stimulates white blood cell production, used to treat or prevent neutropenia
Adalimumab (Humira)	Adalimumab-atto (Amjevita)	9/23/2016	Inhibits TNF-alpha, used in inflammatory disorders
	Adalimumab-adbm (Cyltezo)	8/25/2017	
Etanercept (Enbrel)	Etanercept-szzs (Erelzi)	8/30/2016	Inhibits TNF-alpha, used in inflammatory disorders
Infliximab (Remicade)	Infliximab-dyyb (Inflectra)	4/5/2016	Inhibits TNF-alpha, used in inflammatory disorders
	Infliximab-abda (Reflexis)	4/21/2017	
Bevacizumab (Avastin)	Bevacizumab-awwb (Mvasi)	9/14/2017	Vascular endothelial growth factor angiogenesis inhibitor used in oncology
UNDER DEVELOPMENT			
Reference Name	**Companies Developing Biosimilars**		**Therapeutic Action/Use**
Cetuximab	Amgen		Epidermal growth factor receptor antagonist used in oncology
Erythropoetin-alpha	Hospira		Stimulates red cell production, used in anemia
Filgrastim	Apotex		Stimulates white blood cell production, used to treat or prevent neutropenia
Pegfilgrastim	Apotex, Sandoz, Coherus, Novartis		Stimulates white blood cell production, used to treat or prevent neutropenia
Trastuzumab	Novartis		HER2 receptor antagonist used in oncology

associated with insurer reimbursement, manufacturer reporting requirements, and manufacturer data reporting.[1] When giving drugs that cost thousands or tens of thousands of dollars per dose, proper storage (see sidebar), and education of other clinicians and patients about proper handling and administration is critical. Similar to small molecule drugs, adherence is poor for biologic medications with 35% to 42% nonadherence rates for the most commonly used biologic drugs. Pharmacists have a major role in enhancing patient adherence that is being utilized in some settings but could be expanded to optimize patient outcomes.[5]

Like "AB" rated small molecule generics, the FDA believes that interchangeable biologic products can be automatically substituted for the reference product without the prescriber intervention, where a drug that is biosimilar would need to be specifically prescribed in order to be dispensed.[17] Many states have their own regulations about automatic interchangeable biologic product substitution which run the gamut from states where the pharmacist may substitute (with various stipulations) to states where they must substitute. And, some states still have no regulations at all.[23] **Table 3** summarizes the basics of state regulation concerning interchangeable biologic substitution[23] It is important to remember that a biosimilar has

Sidebar: Biologic Storage

- Each biologic's prescribing information (package insert) give specific storage directions. Usually, these agents require refrigeration.
- Pharmacists and pharmacy technicians should review storage directions with patients. Patients can keep some biologics at room temperature for short periods of time, but pharmacists and pharmacy technicians need to coach patients about these temperature excursions. Some biologics cannot be returned to the refrigerator after excursions and must be discarded.
- Patients need very specific information about storage for biologics. Pharmacists and pharmacy technicians need to tell patients not to leave this products in their cars unless they are in coolers.
- Traveling is a specific concern. Check each product's package insert for information about what to do while traveling. Some manufacturers provide free travel coolers, and instruct patients how to navigate airport security with carry-on luggage.

to be proven interchangeable with an innovator biologic drug for a specific indication. Some innovator biologic drugs may be indicated for multiple diseases but the interchangeable biologic product has only been proven to meet the criteria for one of them. In this case automatic substitution for the other indications would not be consistent with FDA guidance.[17] Unfortunately, the FDA has not approved any interchangeable biologic products at the moment so the procedure is academic.

With seven available biosimilars at this time, pharmacists in regular or specialty pharmacies can have a critical roles in enhancing their utilization. The pharmacist in a specialty pharmacy can either contact a prescriber to alert them of the availability of a biosimilar product or educate the patient about its availability. This could be especially useful for patients struggling to afford their medications, which is becoming increasingly common. In addition, patients have the right to have a voice in important healthcare decisions.

Community pharmacists likewise can feel the negative repercussions of patients with high deductibles, high tiered copayments, or who pay a flat percent of the biologic drug's cost. Patients may prioritize biologic therapy over their small molecule therapies for common diseases like hypertension and hyperlipidemia for financial reasons. Alerting them or their prescribers of a lower cost alternative is prudent. Similarly, a payer (insurer or governmental organization) might require step therapy with failure of biosimilar before allowing coverage of the reference drug. Insurers may also employ tiered formularies with different copayments or levels of coinsurance for biosimilar and reference biologic drugs to incentivize the lower cost options.

Pharmacists in specialty pharmacies also need to review the package inserts to be sure they appreciate all differences between the innovator biologic and the biosimilar product and can communicate those differences to the prescriber or the patient.

PAUSE AND PONDER:
Look at the table of relevant state laws on the next page.

What laws apply to you?

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CONCLUSIONS

Many patients struggle to afford their medications in the United States. Generic drugs have been a welcome blessing in curtailing drug costs in the traditional small molecule drug market with strong utilization and acceptance. Pharmacists play a major role in enhancing the acceptance of both prescribers and patients.

Biologic agents bring increased specificity to patient care and can allow better patient results but they are very expensive. Current regulations governing interchangeable biologic products and biosimilars could have an important impact on bending the cost curves down to more sustainable levels. However, even if many options were available, the cost savings look to be much more modest than was seen with generic small molecule drugs.

Pharmacists in traditional or specialty pharmacy have an important role in enhancing patient safety and efficacy when they take both small molecule or biologic drugs. The advent of interchangeable biologic products and biosimilars will provide an additional tool to help optimize care through enhanced affordability. Similarly, pharmacists in managed care need to utilize methods to incentivize the use of interchangeable biologic products or biosimilars. These interventions will help their customers and the patients to continue to be able to afford their coverage.

Table 3. State Law Allowing Automatic Substitution of FDA Designated Interchangeable Biological Products.[23]

State	Must be FDA Designated as Interchangeable	Physician Must Not Have Instructed No Substitution	Physician Must Prospectively Approve Substitution	Physician Alerted and/or Documented in Medical Record ¥	Patient/Person Presenting Prescription Must be Informed of Substitution	Patient Must Approve or Not Refuse Substitution £	Substituted Drug Must Be of Lower/Lowest Cost
PHARMACIST MAY SUBSTITUTE							
Arizona	✓	✓		✓	✓		
California	✓	✓		✓	✓		✓
Colorado	✓	✓		✓	✓		✓
Delaware	✓	✓		✓	✓		
Florida	✓	✓		✓	✓		
Georgia	✓	✓		✓			✓
Hawaii	✓	✓		✓	✓	✓	
Idaho	✓	✓		✓			
Illinois	✓	✓		✓	✓		
Indiana	✓		✓	✓	✓		
Louisiana	✓	✓		✓	✓	✓	
Massachusetts	✓	✓		✓	✓		
Missouri	✓	✓		✓	✓		✓
New Jersey	✓	✓		✓			
North Carolina	✓	✓		✓			
North Dakota	✓	✓		✓	✓	✓	
Oregon	✓	✓		✓	✓		
Pennsylvania	✓	✓		✓	✓		
Puerto Rico	✓			✓	✓	✓	
Tennessee	✓	✓		✓	✓		
Texas	✓	✓		✓	✓	✓	✓
Utah	✓		✓	✓	✓		
Virginia	✓	✓		✓	✓	✓	
PHARMACIST MUST SUBSTITUTE							
Kentucky	✓			✓			✓
Rhode Island	✓	✓		✓	✓	✓	
Washington	✓	✓		✓	Sign Posted	✓	✓

¥ denotes that the time from dispensing to notification varies from state to state (as soon as reasonable to 2-5 days in many cases).

£ denotes that patients either have to give assent or have to refuse substitution whether or not they are prospectively informed. More specific information is available in reference 23 or by contacting the individual State Boards of Pharmacy.

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