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BIOLOGICS AND STATE SUBSTITUTION LEGISLATION:
WHY STATES SHOULD ENACT INTERCHANGEABLE BIOLOGIC SUBSTITUTION LAWS NOW

By Pat A. Cerundolo, November 24, 2014[1]

The Biologics Price Competition and Innovation Act of 2009 ("BPCIA") authorizes the Food and Drug Administration ("FDA") to oversee an abbreviated approval pathway for biologics that are either "biosimilar" to, or "interchangeable" with, reference biologics already approved.[2] Unlike "small molecule" drugs that are chemically synthesized and structurally well-defined, biologics are generally derived from living material and are structurally complex. Since the 1970s, state laws have controlled the substitution of small molecule generic drugs for prescribed brand name drugs. With the enactment of the BPCIA, states are beginning to address the substitution of interchangeable biologics. The following discusses key questions and issues bearing on state legislative policy addressing this issue.

I. NO FURTHER FDA GUIDANCE IS NECESSARY FOR ENACTING INTERCHANGEABLE BIOLOGIC SUBSTITUTION LAWS

The BPCIA interchangeability standards should be sufficient for designing state legislation. Under the BPCIA, FDA is authorized to approve only two categories of biologics that are evaluated against a reference biological product: biologics that are "biosimilar" and biologics that are "interchangeable."[3] Of these, only "interchangeable" biologics are suitable for substitution without physician intervention.[4] The BPCIA's standard should be sufficient for formulating workable and unambiguous state laws that restrict biologic substitution to products that FDA determines to be "interchangeable." Many state laws controlling the substitution of small molecule generic drugs currently permit substitutions for drugs determined to be "therapeutically equivalent" by FDA, without further reference to any other FDA guidance.[5]

An FDA "list" of interchangeable biologics should not be necessary for crafting state biologic substitution laws. Approximately forty states had already enacted generic drug substitution laws before FDA first developed an official list of therapeutically equivalent small molecule drugs, otherwise known as the "Orange Book," in 1980.[6] State interchangeable biologic substitution legislation can similarly incorporate and rely on FDA "interchangeability" determinations as they are published. For example, a provision of the Massachusetts generic drug substitution laws (as last amended in 1976) requires the state's formulary of interchangeable generic drugs to include "the list of drugs determined by the regulation of [FDA] to be therapeutically equivalent and interchangeable *when said list becomes available*."[7]

In fact, FDA has already issued, and will continue to update, its "Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity and Interchangeability Evaluations," which will informally be known as the "Purple Book."[8] This reference volume will enable pharmacists, among other users, "to see whether a biological product licensed under [the BPCIA] has been determined by FDA to be biosimilar to or interchangeable with a reference biological product."[9]

FDA interchangeability guidance may not be finalized until after the first biosimilar approvals. The BPCIA expressly provides that FDA's issuance or non-issuance of guidance shall not preclude its review of, or action on, biosimilar license applications.[10] As of earlier this fall, FDA has already held 59 initial meetings with, and received at least 18 Investigational New Drug Applications from, companies developing biosimilars.[11] Final clinical trials for numerous biosimilar products are also well under way.[12] In any event, FDA's biosimilars guidance should not control the actual procedures for substitution of interchangeable biologics at the state level. Instead, FDA is focused on the scientific and clinical considerations bearing on biosimilars development. For example, FDA summarized its initial draft biosimilars guidance as its "current thinking on key scientific and regulatory factors involved in submitting applications for biosimilar products to the agency," including scientific and quality considerations in demonstrating biosimilarity to a reference biological product.[13] FDA notes that its more recently issued guidance is "intended to assist sponsors in designing clinical pharmacology studies that can support an application for FDA's approval of a biosimilar."[14] Any future FDA guidance on interchangeability is also likely to focus on scientific and clinical considerations for approval. However, given FDA's explicit authority under the BPCIA to approve and designate which biologics are "interchangeable" and thus appropriately substitutable, no additional FDA guidance should be necessary for the development of state biologic substitution policy. As noted, many existing state laws controlling the substitution of generic drugs do not expressly rely on detailed FDA guidance other than referencing FDA's therapeutic equivalency determinations.[15]

II. THE BPCIA DOES NOT PREVENT STATES FROM ENACTING INTERCHANGEABLE BIOLOGIC SUBSTITUTION LAWS

Drug substitution continues to be regulated by the states. FDA has long acknowledged state authority over drug substitution practices.[16] Since the enactment of the first state generic drug substitution laws, FDA has confirmed that its published therapeutic equivalency guidance is "advice to the public and to the [s]tates" and "in no way relieves practitioners of their professional duty to prescribe and dispense drug products with due care to individual patients."[17] There have been no changes in any applicable laws, regulations, or guidances that would reverse this longstanding position with regard to federal versus state jurisdiction, or otherwise seek to have FDA or any other federal agency encroach on state governance of the substitution process at the pharmacy level. Although the BPCIA provides that an

interchangeable biologic "may be substituted for the reference product without the intervention of" the prescribing physician, by its own terms this clause is not inconsistent with state laws that would continue to guide the substitution process by requiring pharmacists to communicate with prescribers and patients about those substitutions and maintain related records.[18]

III. PENDING LEGISLATIVE PROVISIONS ON PATIENT NOTICE, PHARMACY-PRESCRIBER COMMUNICATIONS, AND RECORD KEEPING ARE CONSISTENT WITH MANY EXISTING STATE LAWS

Legislation pending in many states would require pharmacists to communicate with prescribers, notify patients, and keep related records when dispensing interchangeable biologics. Such proposals adopt generic drug substitution procedures already required under many existing state laws. Most states already require patient notification of, or consent for, the substitution of generic drugs.[19] Some states already require pharmacists to communicate with prescribers about generic drug substitutions in certain circumstances.[20] All states already have laws requiring pharmacists to maintain prescription dispensing records for certain minimum periods, and many specifically require pharmacists to maintain drug substitution records.[21]

Existing state substitution laws do not clearly apply to biologics. Although all states have laws regulating generic drug substitution, all were enacted before the BPCIA's establishment of an approval pathway for interchangeable biologics. In fact, in many states, FDA's "therapeutic equivalence" determinations as published in the "Orange Book" presently control a pharmacist's substitution selections.[22] Therefore, existing drug substitution laws in many cases are designed to reflect interchangeability standards applicable to generic drugs, and not biologics. For this reason, many states will require new legislation updating their laws to clearly authorize pharmacists to substitute interchangeable biologics.

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[1] This paper updates earlier versions dated March 14, 2013 and January 3, 2014.
[2] Section 351(k) of the Public Health Service Act, at 42 U.S.C. § 262, enacted as part of the Affordable Care Act.
[3] 42 U.S.C. § 262(k).
[4] 42 U.S.C. § 262(i)(3).
[5] In the context of small molecule drugs approved under the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 301 *et seq*.), FDA deems a generic drug that is "therapeutically equivalent" to its brand name counterpart as interchangeable with that drug. *See* FDA "Orange Book," 32d Ed., Preface; s*ee also* Therapeutically Equivalent Drugs, 44 Fed. Reg. 2932, 2937 (1979) (discussing relationship between therapeutic equivalency and interchangeability); *see, e.g.,* 35 P.A. STAT. ANN §960.2; S.D.CODIFIED LAWS §36-11-2(12); VT.STAT.ANN. §4605(a)(all providing that FDA therapeutic equivalency determinations shall serve as the basis for generic drug substitutions).
[6] 44 Fed. Reg. at 2932. Prior to the first publication of the Orange Book, states had limited information available to guide prudent drug product selection, and would attempt their own, state-specific therapeutic equivalence determinations with FDA's *ad hoc* assistance. James E. Knoben, Scott, G.R., Tonelli, R.J., "An overview of the FDA

publication 'Approved Drug Products with Therapeutic Equivalency Evaluations,'" *Am J Hosp Pharm*. 1990 Dec;47(12):2696-700.

[7] MASS.GEN.L. c. 17, § 13 (emphasis supplied); *see also* Mass.Gen.L. c. 112, §12D.

[8] Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations, available at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm411418.htm

[9] *Id.*

[10] 42 U.S.C. § 262(k)(8)(C). Although FDA is currently developing such guidance, FDA has recently stated it plans to review initial biosimilar applications prior to issuing any product specific guidance. Catherine Larkin and Anna Edney, *U.S. Biosimilar Market Won't Wait for Product-Specific Guidance* (Interview with Janet Woodcock, Director of FDA's Center for Drug Evaluation and Research), *Bloomberg*, Feb. 12, 2013.

[11] Anna Edney, *$250 Billion in Biotech Drug Savings on Brink of Arrival*, Bloomberg News, Sep. 13, 2014, available at http://www.bloomberg.com/news/2014-09-12/-250-billion-in-biotech-drug-savings-on-brink-of-arrival.html; Alex Philippidis, *Following Up on Follow-On Biologics*, GEN Exclusives, Nov. 12, 2013, available at http://www.genengnews.com/insight-and-intelligence/following-up-on-follow-on-biologics/77899951/ (accessed Jan. 3, 2014).

[12] http://www.sandoz.com/media_center/press_releases_news/global_news/2014_04_28_biosimilars_milestones.shtml; http://www.gabionline.net/Biosimilars/News/Amgen-starts-phase-III-trial-for-biosimilar-rituximab; *Amgen, Hospira and Sandoz set to dominate US biosimilars market*, GaBi Online, May 31, 2013, available at http://www.gabionline.net/layout/set/print/content/view/full/2584 (accessed Jan. 3, 2014).

[13] FDA Release: FDA Issues Draft Guidance on Biosimilar Product Development, Feb 9, 2012.

[14] Guidance for Industry, Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product (May, 2014), at 1.

[15] *See supra,* n.5.

[16] *See* 44 Fed. Reg. at 2933 (noting that "establishing requirements for pharmacies" is a state "regulatory activity pertaining to health care delivery").

[17] *See* Therapeutically Equivalent Drugs; Availability of List, 45 Fed. Reg. 72582, 72587, 72589 (1980) (describing the scope and legal effect of FDA's therapeutic equivalency determinations); *see also* FDA "Orange Book," 32d Ed., Preface ("Therapeutic equivalence evaluations in the publication are not official FDA actions affecting the legal status of products under the [Federal Food Drug and Cosmetic Act]").

[18] 42 U.S.C. § 262(i)(3).

[19] *See* NATIONAL ASSOCIATION OF BOARDS OF PHARMACY. 2013. Survey of Pharmacy Law ("NABP Survey"), 65; *see, e.g.*, FLA. STAT. ANN. §465.025(3)(a); N.H. REV. STAT. ANN. §146-B:2:IV; 35 PA. STAT. ANN. §960.3(b); S.C. CODE. ANN. §39-24-40(E); S.D. CODIFIED LAWS §36-11-46.3; TEX. OCC. CODE §562.009(a)(2).

[20] *See* CONN. GEN. STAT. §20-619(b),(i)(requiring pharmacists to notify practitioners of drug substitutions "at the earliest reasonable time," and requiring written consent from practitioners for anti-epileptic drug substitutions); HAW. REV. STAT. §328-92(c) & TENN. CODE. ANN. §53-10-210(b)(requiring pharmacists to obtain consent of prescribing practitioner for substitutions of anti-epileptic drugs).

[21] *See* NABP Survey, at 70; FLA. STAT. ANN. §465.025(4); GA. CODE. ANN. §26-4-81(d)(1); HAW. REV. STAT. §328-94; 35 PA.STAT. ANN. §960.3(d); S.C. CODE. ANN. §39-24-40(D); VA. CODE. ANN. §54.1-3408.03.C; W. VA. CODE §30-5-12b(h).

[22] *See, e.g.,* 35 P.A. STAT. ANN §960.2; TENN. CODE. ANN. §53-10-208(a); 18 V.S.A. §4605.