

The Inevitability of Interchangeability

A genuine concern for follow-on biologic drug applicants is that chemically dissimilar follow-on biologics (e.g., those produced in distinct cell lines and/or by distinct biochemical methods) will have extreme difficulty gaining U.S. Food and Drug Administration (FDA) sanctioned “interchangeability” to a reference biologic product.¹ Despite major advances in protein analytics, it is the *process* of making a biologic product that largely defines the biologic drug product.² Non-interchangeable “biosimilar” products are not available for automatic pharmacy substitution or market exclusivity and may have difficulty gaining market share due to perceived safety and efficacy concerns.³ Moreover, while it is true that distinct biopharmaceutical manufacturing processes invariably yield distinct biopharmaceuticals with meaningful differences from a chemical and structural perspective, do such changes necessarily equate with meaningful differences from a clinical perspective?⁴ We think not.

Fortunately for follow-on biologic drug manufacturers, biological interchangeability does not presuppose biological duplication. Human physiology is tolerant. It has evolved to either ignore, or accept and treat as equal, certain alterations and/or redundancies in chemical structure.⁵ For example, while all amino acids are chemically distinct, certain amino acids (and by extension certain post-translational modification) are so structurally similar that conserved substitutions can be made without detectable differences in physiologic or pharmacologic activity.⁶ Put simply, protein *structure/function* is more conserved than protein *sequence*. Structurally and chemically diverse biologics can have nearly identical pharmacologic activity.⁷ For those considering incorporating interchangeable follow-on biologics into their corporate business strategy, we have compiled a preliminary list of reasons why

¹ See 42 U.S.C. §262(i)(3) as amended “[t]he term 'interchangeable' or 'interchangeability' . . . means that the biological product

² Put another way, two different processes cannot make the same biological product. While contemporary analytical methods may not allow for complete chemical/structural characterization of many biological products, FDA has shown historical interest in using analytical data when permitting a sponsor to rely on clinical data from a reference product for “comparable” biologics made by different manufacturing processes. See

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm122879.htm>

³ See Henry Grabowski et al., *The Market for Follow-on Biologics: How Will It Evolve?*, 25 *HEALTH AFF.* 1291, 1298 (2006) (suggesting that physicians and patients will be slow to accept biogeneric [i.e., interchangeable] products that are not thought to be “therapeutically equivalent” to the innovator product and that this phenomenon will add to the cost of producing follow-on biologics).

⁴ Chemically distinct biologics are by definition structurally distinct. Biological products made in different quantities, by improved methods, with different reagents and/or in different locations (even by the same manufacturer) can additionally be both pharmacologically and immunologically distinct. See CDER Summary Review of BLA125291 (requiring separate approval of Myozyme™ and Lumizyme™, alglucosidase alfa, due to bioreactor scale-up from 160L to 2000/4000L, respectively). See also Casadevall, N., “Immune-response and adverse reactions: PRCA case example”, http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2009/11/WC500011064.pdf

⁵ As an extreme and biologically fundamental example, the human genetic code is interchangeable. Chemically distinct DNA codons and their corresponding tRNA molecules are functionally interchangeable with other codons and tRNAs, respectively. With respect to the synthesis of an amino acid sequence, there are over 10⁴⁹ distinct nucleic acid species that are interchangeable with respect to encoding an identical cytochrome c protein.

⁶ For example, serine and threonine are often biologically substitutable as are aspartic acid and glutamic acid.

⁷ “The Combined Effects of Amino Acid Substitutions and Indels on the Evolution of Structure within Protein Families”, Z. Zhang, et al., *PLoS One*. 2010; 5(12): e14316, published online December 13, 2010.

interchangeable biologics are a scientific and regulatory inevitability.⁸ Ultimately, follow-on biologic drug applicants must determine if seeking interchangeability over biosimilarity makes business sense.⁹

Background

Prior to 1970, pharmacists were legally prevented from substituting generic small molecule drugs for prescription brand name drugs. In the decade that followed, most states began passing drug-product substitution laws allowing automatic substitution a generic drug even when the prescription called for a brand-name drug. A watershed event for the generics industry occurred in 1984 with the passage of the Hatch-Waxman Act whereby the manufacture and regulatory approval of interchangeable small molecule drugs became less expensive and more profitable.¹⁰

With the passage of the Patient Protection and Affordable Care Act (PPACA) in 2010, a conceptually similar situation is currently unfolding in the realm of protein based pharmaceuticals.¹¹ While interchangeable biologic drugs are now a legal reality, some doubt that they will ever become a practical reality.¹² These dour conclusions may be premature. In this brief, we provide several plausible reasons why interchangeable biologics will become a lucrative market reality in the near future.¹³ While any individual rationale may not support a *per se* claim of interchangeable inevitability, the cumulative effect of multiple overlapping reasons may accomplish this goal.

Reason 1: FDA Historical Willingness to Approve Biologically Complex Interchangeable Drugs

For historical reasons, certain protein drug products and a few moderately complex non-protein drugs were approved under the FD&C Act.¹⁴ As such, follow-on versions of these chemically and structurally variable drugs are legally available for approval either under the §505(b)(2) or §505(j) drug pathways, the latter being fully interchangeable (i.e., “generic”) with reference drug.¹⁵ Fully interchangeable §351(k) follow-on biologics are the FDA’s legal and scientific equivalent of small molecule §505(j) generic “ANDA” drugs with one very expensive distinction.¹⁶ Unlike traditional

⁸ We exclude any obvious consumer cost savings resulting from interchangeable follow-on biologics.

⁹ While this aspect is not discussed here, such factors could include: (i) market size, (ii) pricing, (iii) date of market entry, (iv) presence of other biosimilars and/or interchangeables, and (v) patent and marketing exclusivity periods.

¹⁰ Also known as the Drug Price Competition and Patent Term Restoration Act of 1984. This act eliminated expensive clinical trials for bioequivalent versions of comparatively non-complex small molecule drugs.

¹¹ While there are obvious differences between the two regulatory schemes, the unifying theme of both pieces of legislation is to provide the public with less expensive pharmaceuticals while maintaining a financial incentive for innovative research and development.

¹² See D. Gingery, “Waxman Says Biosimilar Pathway Will Push Applicants To BLA”, Pink Sheets, November 22, 2010 (remarking “I can’t imagine there’s going to be a clamor for approval of [bio]generics . . .”).

¹³ While this article does not focus on the less rigorous standard of “biosimilarity”, it can be assumed that any “interchangeable” biologic will also be a “biosimilar” biologic. How “biobetters” will impact follow-on biologic business decisions is outside the scope of this article.

¹⁴ For example, VprivTM (human velaglucerase alfa) was approved in 2010 under the FD&C Act despite being comprised of the 523 amino acid β-glucocerebrosidase protein. The 497 amino acid mature form is variably glycosylated. LovenoxTM (enoxaparin sodium) was approved in 1993 as an NDA and is composed of a complex mixture of low molecular weight non-protein glycosaminoglycans isolated from animal tissue. CopaxoneTM (glatiramer acetate), approved under the FD&C Act in 1996 for the treatment of relapsing-remitting multiple sclerosis, is composed of low molecular weight peptides. Insulin, a relatively simple 5 kDa protein, and its various analogues, was also approved under the FD&C Act via a New Drug Application (NDA).

¹⁵ See 21 U.S.C. §355. §505(b)(2) approved drugs are chemically distinct drugs and are often not interchangeable with a reference drug. §505(j) “ANDA” drugs are fully interchangeable with a reference drug product. See www.fda.gov/downloads/Training/ForHealthProfessionals/ucm090402.pdf.

¹⁶ Interchangeable biologics and generic drugs are regulated under the PHS Act and the FD&C Act, respectively.

generic drugs, FDA approval of §351(k) interchangeable biologic drugs does not disallow the submission of clinical trial data demonstrating interchangeability.¹⁷

FDA has shown a historical willingness to approve interchangeable versions of incompletely characterized protein drug products.¹⁸ Menotropin (human menopausal gonadotropin) is a protein hormone drug comprising follicle-stimulating hormone (FSH) and luteinizing hormone (LH) for the treatment of fertility pathologies.¹⁹ PergonalTM was one of two approved menotropin drugs at the time FDA conceded that RepronexTM has the identical amino acid sequence as PergonalTM, but with a different glycosylation profile.²⁰ Despite a conclusion that absolute chemical identity would be impossible due to the inherent glycosylation microheterogeneity of *both* the reference and generic products, FDA approved RepronexTM under §505(b)(2) as having the “same” active ingredient as PergonalTM.²¹ Notably, FDA had originally approved two fully generic §505(j) versions of menotropins in 1997.²² In 1998, another §505(b)(2) drug, GlucaGenTM (recombinant glucagon by NovoNordisk), was approved only after inclusion of clinical trial data from a crossover study with glucagon USP (Eli Lilly).^{23,24}

Further setting the stage for approval of follow-on biologics, in 2006 FDA approved a §505(b)(2) application for OmnitropeTM as a non-interchangeable follow-on version of Pfizer’s pioneer recombinant human growth hormone protein product.²⁵ Other examples of similarly approved protein-based drugs include HylenexTM (recombinant hyaluronidase) and ForticalTM (recombinant calcitonin) based on the pioneer drugs WydaseTM (Baxter Healthcare) and MiacalcinTM (Novartis), respectively.²⁶ In 2010, FDA took a considerable step forward with the approval of a 505(j) generic drug application for the complex non-protein drug LovenoxTM (enoxaparin sodium).²⁷ On September 19, 2011, FDA approved a second

¹⁷ See 42 U.S.C. §262(k)(4)(B) as amended. Sponsors will likely need to submit clinical data from “switchover” or “crossover” studies. Such studies administer the follow-on biologic to patients previously exposed to the reference biological drug. For the foreseeable future, the degree of clinical trial data required by FDA will likely be approved on a case-by-case basis and dependent on drug class and/or mechanism(s) of action.

¹⁸ See *Serono Labs, Inc. v. Shalala*, 158 F.3d 1313, 1316 (D.C. Cir. 1998). One notable exception has been FDAs unwillingness to approve a 505(j) generic version of the incompletely characterized conjugated estrogen product PremarinTM.

¹⁹ Human FSH (i.e., follitropin) is a 33kDa hormone dimer composed of a 92 amino acid α -subunit and a 111 amino acid β -subunit. Human LH is a 26kDa hormone heterodimer. Importantly, both proteins are variably glycosylated.

²⁰ Protein glycosylation is a major source of follow-on biologic heterogeneity. *Id.* at 1317-1318.

²¹ *Id.* at 1318 (explaining that “complete chemical identification of all the carbohydrate variants in a protein product often is not possible or feasible . . . [and] appear *not to be clinically significant* for the product’s intended uses.”)

²² ANDA Nos. 073598 and 073599 (menotropins), injectable, 75 and 150 IU/vial (Ferring Pharmaceuticals). These generic menotropin drugs were characterized by FDA as “equivalent to PergonalTM.” See CDER Medical Review(s), NDA121047, page 22. These drugs currently have a discontinued marketing status.

²³ Notably, FDA made explicit that while GlucaGenTM and Lilly USP Glucagon “are therapeutically equivalent . . . any claim of bioequivalence with Lilly USP glucagon should be rejected.” See CDER Medical Review, Application number 020918, page 22. Suggestively, FDA concluded that “no clinical relevance” exists if an inadvertent branded drug switch were to occur between Lilly USP glucagon and GlucaGenTM. See CDER Chemical Review, Application number 020918, electronic page 7. On the other hand, fully generic versions of glucagon, initially approved under 505(j) (ANDAs 071022 and 071023), have since been discontinued.

²⁴ The language of the PPACA suggests that crossover/switchover clinical trials will play a significant role in approving interchangeable follow-on biologics. See 42 U.S.C. §262(k)(4)(B) as amended (“the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch.”)

²⁵ Based on Pfizer’s reference drug GenotropinTM (human growth hormone), a 191 amino acid non-glycosylated peptide. To be clear, OmnitropeTM is not an interchangeable drug product (e.g., “BX” rating) - substantial clinical trial data was required for approval.

²⁶ See <http://www.fda.gov/NewsEvents/Testimony/ucm154070.htm> (“[n]o hyaluronidase product is rated by FDA as therapeutically equivalent (that is substitutable) to any other approved hyaluronidase product.”) Notably, FDA states that ForticalTM and MiacalcinTM are not interchangeable. See Chemistry Review for NDA-21-406, page 9

²⁷ Generic enoxaparin sodium, being a 505(j) ANDA generic (here, ANDA No. 77-857, approved July 23, 2010), is fully substitutable. See “United States FDA Approval Of Generic Lovenox®: A First Glimpse At Follow-On Biologic Sameness”,

generic LovenoxTM product based on Amphastar Pharmaceutical's Abbreviated New Drug Application (ANDA) for enoxaparin sodium.²⁸

To clarify, the above examples are not truly interchangeable *biologics* as defined in §351(k) of the PPACA because they either are: (i) a biologic, but not interchangeable (e.g., OmnitropeTM) or (ii) interchangeable, but not a true biologic (e.g., enoxaparin sodium). Despite these differences, these approvals cast a favorable light on the willingness of FDA to approve fully interchangeable versions of incompletely characterized, and biologically complex, reference drug products.²⁹

Reason 2: Distinct Biological Products Are Successfully Being Used Interchangeably

To gain interchangeable marketing status under the PPACA, follow-on biologic applicants will almost certainly (at least initially) have to successfully complete conventional “switchover” trials.³⁰ Alternatively, under the Expanded Access Program, FDA may forgo formal switching studies and allow access to unapproved investigational drugs “to patients with serious diseases or conditions when there is no comparable or satisfactory alternative therapy . . . to treat the patient’s disease or condition.”³¹

Gaucher’s disease is a chronic congenital disorder of lipid metabolism caused by a deficiency of the enzyme beta-glucocerebrosidase. Enzyme replacement therapy (ERT) involves extended palliative administration of exogenously produced enzyme.³² There are three FDA approved ERTs for Gaucher’s disease: CeredaseTM (alglucerase, Genzyme), CerezymeTM (imiglucerase, Genzyme) and VprivTM (velaglucerase alfa, Shire).³³ A fourth ERT monotherapy, ElelysoTM (taliglucerase alfa, Protalix) was approved on May 1, 2012.³⁴

Viral contamination of a Genzyme manufacturing plant resulted in severely decreased production of imiglucerase precipitating a subsequent global shortage of biological products for treating Gaucher’s disease. Under the Expanded Access Program, Gaucher’s patients formerly taking CerezymeTM were switched to VprivTM or ElelysoTM with no reported serious adverse events. Dedicated switchover trials from CerezymeTM to VprivTM or UplysoTM have additionally demonstrated impressive safety and efficacy profiles.³⁵ Building on these successes, encouraging results have also been observed with ElelysoTM in a long-term expanded access trial for patients previously treated with imiglucerase.³⁶

Fabry’s disease is another enzyme deficiency disorder resulting from a deficiency in alfa-galactosidase A. Like Gaucher’s, the current approved treatment for Fabry’s disease is enzyme

www.tblawadvisors.com, Summer 2010. It is the opinion of these authors that a similar generic fate awaits the peptide drug CopaxoneTM.

²⁸ ANDA No. 76-684.

²⁹ Unlike the United States, any European follow-on version of branded low molecular weight heparin (LMWH) can only achieve non-interchangeable status and must include clinical studies. See EMEA/CHMP/BMWP/118264/2007, “Guideline On Non-Clinical And Clinical Development Of Similar Biological Medicinal Products Containing Low-Molecular-Weight-Heparins”, Committee For Medicinal Products For Human Use (CHMP), 19 March 2009.

³⁰ Alternatively known as “crossover” trials. Such trials are specifically designed in advance to gauge the interchangeability of a follow-on biologic in patients who have previously taken the branded biologic. See also 42 U.S.C. 262(k)(4), as amended, for statutory language related to interchangeability studies.

³¹ See 21 C.F.R. §§312.300-20. The underlying premise is that FDA would not allow switching if safety and efficacy issues were of any serious concern.

³² Such administration is often intravenously and usually for the entire life of a patient.

³³ Interestingly, the three enzyme replacement therapies were individually approved (in years 1991, 1994 and 2010, respectively) under the NDA pathway despite being protein therapeutics of a considerably large molecular weight.

³⁴ Previously known as Uplyso.

³⁵ ClinicalTrials.gov Identifiers: NCT00478647, NCT00712348 and NCT00705939.

³⁶ ClinicalTrials.gov Identifier: NCT00962260.

replacement therapy. There are two available products, Fabrazyme™ (agalsidase beta) and Replagal™ (agalsidase alfa). An extended shortage of Fabrazyme™ has necessitated a large number of patients switch from Fabrazyme™ to Replagal™.³⁷ To the assurance of follow-on biologic product manufacturers, such examples will likely soften FDA's stance on fully interchangeable biologics and provide inroads for establishing *de facto* interchangeability in the United States.³⁸

Reason 3: Drifted Interchangeable Biologics

The chemical identity of a biological drug product will invariably “drift” away from its FDA approved analytical specifications. The likely result will be a biosimilar biologic with detectable chemical and structural differences, yet no discernable pharmacologic differences.³⁹ Biological drift can occur during intentional commercial scale-up and refinement of the manufacturing process (i.e., “active biodrift”) or as a result of lot-to-lot variability (i.e., “passive biodrift”).⁴⁰ Approved biologics having undergone either form of biological “drift” and currently marketed with identical labels would appear to be yet another *de facto* satisfaction of the PPACA requirements for an interchangeable biologic.⁴¹

A major financial concern for interchangeable biologic manufacturers is the near certain requirement of clinical trial data proving interchangeability.⁴² As early as 1990, FDA's Center for Biological Evaluation and Research (CBER) published industry guidance stating that submission of clinical trial data for approval of “comparable” follow-on biologics are *not* always necessary. In this document, CBER noted that “significant changes in the manufacturing process [of cytokine products] . . . *may* result in the need to conduct additional . . . clinical studies.”⁴³ Six years later, FDA concluded that branded biological drugs having undergone manufacturing changes may be considered “comparable” with the reference biological *without conducting additional clinical trials* if comparability test data demonstrates that the product after the manufacturing change is safe and effective.⁴⁴ Such manufacturing

³⁷ ClinicalTrials.gov Identifier: NCT01268241. Shire representatives have stated publically that switched patients have been “very satisfied”, even after 18 months. See “Despite Rival's Supply Problems, No Guarantee That Shire Will Re-File Replagal In U.S.”, The Pink Sheet, April 13, 2011.

³⁸ Interchangeable crossover studies are not unique to the United States. Crossover clinical trials were instrumental in the European Medical Agency's approval of Retacrit™ – a biosimilar erythropoietin product. See Retacrit: EPAR-Scientific Discussion, published Jan. 15, 2008, WC500054374, p. 14 “Pharmacokinetics.”

³⁹ See <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm122879.htm> ([m]anufacturing changes may result in no observed alteration in a product. Alternatively, a minor alteration . . . can have either no effect or a substantial effect on the pharmacology of the product. Likewise, a major alteration . . . can have either no effect or a substantial effect on the pharmacology of the product.) A well-known example of a “substantial effect” on product pharmacology involved a reformulation of an approved erythropoietin protein product and subsequent adverse events involving pure red cell aplasia (i.e., PRCA).

⁴⁰ Deliberate commercial scale-up often results in significant product variability relative to lot-to-lot variability. See CDER Summary Review of BLA125291. Post-translational protein modifications are a major source of variability.

⁴¹ Viewed broadly, innovators are essentially (unintentionally?) manufacturing and marketing interchangeable follow-on versions of their original product. See 42 U.S.C. §262(k)(4) (allowing FDA to approve a biologic as interchangeable if a sponsor can show that “(i) the biological product - (i) is biosimilar to the reference product; and (ii) can be expected to produce the same clinical result as the reference product in any given patient; and (B) for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch.”

⁴² Often called “switchover” or “crossover” trials. See ClinicalTrials.gov identifier NCT00712348 as an example.

⁴³ Publicly document available upon request from FDA.

⁴⁴ <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm122879.htm> (where, on a case-by-case basis, a biologic drug sponsor may be able to demonstrate product comparability between a biological product made after a manufacturing change and a product made before implementation of the change through different types of analytical and functional testing, with or without preclinical animal testing.) FDA uses the term “comparable” when comparing biologics made from modified manufacturing processes. This language is distinct, yet scientifically analogous to, the PPACA biosimilar language of “highly similar”. See “Worldwide Experience with Biosimilar Development”, M. McCamish and G. Woollett, mAbs 3:2, 209-217, March/April 2011.

process changes have included “changes implemented during the expansion from pilot scale to full scale production, the move of production facilities from one legal entity to another legal entity, and the implementation of changes in different stages of the manufacturing process such as fermentation, purification, and formulation.”⁴⁵ This guidance was significant because it first demonstrated FDA’s willingness to substitute analytical testing in lieu of full clinical trials to demonstrate comparability to a reference listed protein drug product.

Further maturation of FDA policy toward drifted biologics occurred in 2001 when FDA approved Xigris™ (drotrecogin alfa, activated) despite a manufacturing change that resulted in a product with improved clinical activity midway through an ongoing clinical trial.⁴⁶ Here, FDA concluded that the two versions of the biological product were comparable after “extensive analyses” observed “no differences”.⁴⁷ Despite the improved efficacy, the conclusion of comparability may meet the statutory interchangeability standard outlined in the PPACA.⁴⁸ Two years later, FDA came to similar conclusions of comparability when it approved Amevive™ (alefacept) despite a manufacturing site location change during clinical trials.⁴⁹

Finally, post-translational protein glycosylation is one highly variable source of unintended biological drift. Alternatively glycosylated biological products can occasionally display distinct physiochemical and immunological properties relative to the reference biologic. Encouragingly, recent studies have suggested that a degree of pharmacologic latitude may be tolerated with respect to alternatively glycosylated protein drugs currently on the market.⁵⁰ As protein analytics increase in sophistication and decrease in cost, the day may soon come when FDA requires annual post-marketing reanalysis of approved protein drugs to maintain approval status. Accumulated data would arguably set the goalposts for biosimilarity and/or interchangeability of subsequent follow-on biologics.

Reason 4: Congressional Anticipation of Multiple Interchangeable Follow-On Biologics

In 2005, the United States watched Europe implement the first regulatory pathway for the approval of non-interchangeable follow-on biologics.⁵¹ Soon afterwards, two competing US bills

⁴⁵ <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm122879.htm>

⁴⁶ The manufacturing change involved a change in the master cell bank. See FDA, SBA, Clinical Review of drotrecogin alfa (activated), BLA No. 125029/0, pp. 79, 98 and 140. Such an improvement might be considered a “biobetter” in keeping with current follow-on biologic jargon.

⁴⁷ *Id.* FDA did concede that “[g]iven the complexity of the molecule, however, one cannot exclude the possibility of undetected differences.” It is uncertain whether contemporary analytical methods would have revealed differences. See also “The United States Patient Protection and Affordable Care Act of 2010: How Advances in Bioanalytics Might Cloud FDA Approval of Follow-On Biologics”, <http://www.tblawadvisors.com/>, Winter 2010-2011.

⁴⁸ See 42 U.S.C. §262(k)(4)(A) (where interchangeability may be determined for a singly administered biological product if “(A) the biological product - (i) is biosimilar to the reference product; and (ii) can be expected to produce *the same clinical result* as the reference product in any given patient . . .”) [emphasis added].

⁴⁹ See Clinical Pharmacology Review of Alefacept, p. 1. See also Clinical Review of alefacept, p. 86 (concluding that “[b]y pharmacodynamic and clinical criteria alefacept manufactured by Creative Biomolecules appears to be comparable to alefacept manufactured by Biogen.”) Amevive™ is a 115 kDa glycosylated fusion protein.

⁵⁰ See Schiestl M, Stangler T, Torella C, Cepeljnik T, Toll H, Grau R. Acceptable changes in quality attributes of glycosylated biopharmaceuticals. *Nat Biotechnol.* 2011;29(4):310-2. The glycosylated biological drugs studied included etanercept (Enbrel™), rituximab (Rituxan™) and darbepoetin alfa (Aranesp™).

⁵¹ See E.U. Committee for Medicinal Products for Human Use, Guideline on Similar Biological Medicinal Products, CHMP/437/04 (Oct. 30, 2005), at §2.1 (noting that “by definition, similar biological medicinal products are *not generic medicinal products* . . .” and that “[d]ue to the complexity of biological/biotechnology-derived products the generic approach is scientifically not appropriate for these products.”) [emphasis added].

provided for abbreviated pathways for fully interchangeable follow-on biologics.⁵² With the subsequent enactment of the PPACA in 2010, US lawmakers boldly moved beyond the European model by explicitly granting a finite period of market exclusivity to the first interchangeable follow-on biologic.⁵³ Significantly, US lawmakers must have envisioned the eventual approval of numerous interchangeable biologics as *both* competing bills allowed for multiple interchangeable biologics.⁵⁴ Put simply, by providing limited market exclusivity for the *first* interchangeable, one must accept that Congress and FDA anticipated eventual approval of a *second* interchangeable.

Reason 5: Emergence of “Authorized/Branded” Interchangeable Follow-On Biologics

It stands to reason that an approved Biologics License Application (BLA) holder will have a far easier time gaining FDA approval for a “safe, pure and potent” interchangeable follow-on product than would an unrelated corporate entity.⁵⁵ In 1996, FDA approved the biologic AvonexTM (interferon beta-1a) based on clinical trial data transferred from one corporate entity to another.⁵⁶ It should be noted that the two corporations were collaborators and the successful manufacture of the biological product BioferonTM occurred only after an initial failed attempt.⁵⁷ A more striking example involves Sanofi’s authorized generic version of LovenoxTM (AG-Lovenox) sold under its Winthrop U.S. subsidiary. Since its introduction into the market in the fall of 2011, AG-Lovenox has commanded a near 30% market share - largely at the expense of the Sandoz/Momenta generic.^{58,59}

Under the PPACA, a BLA holder (or even a closely related corporate entity) is ostensibly not precluded from acquiring interchangeability exclusivity after expiration of their own reference product 12-year exclusivity period.⁶⁰ That this strategy may be employed is evidenced by language in H.R. 1427 warning that “no holder of a biological product license . . . shall manufacture, market, sell, or distribute a rebranded interchangeable biological product, directly or indirectly, or authorize any other person to manufacture, market, sell, or distribute a rebranded interchangeable biological product, for any condition

⁵² See H.R. 1427, “*The Promoting Innovation and Access to Life-Saving Medicine Act*”, §3(a)(2), § 351(k)(5)(B)–(C) (providing “for a finding . . . that a biological product is (i) interchangeable with a reference product . . .”) See also H.R. 1548 “*The Pathways for Biosimilars Act*”, §101(a)(2), §351(k)(4) (allowing for interchangeability if certain safety standards are met).

⁵³ See 42 U.S.C. §262(k)(6) as amended (“[u]pon review of an application submitted under this subsection . . . the Secretary shall not make a determination . . . that the second or subsequent biological product is interchangeable for any condition of use until the earlier of - (A) 1 year after the first commercial marketing of the first interchangeable biosimilar . . . (B) 18 months after . . . a final court decision . . . (C) . . . (i) 42 months after approval of the first interchangeable . . . if the applicant . . . has been sued . . . or . . . (ii) 18 months after approval of the first interchangeable . . . if the applicant . . . has not been sued . . .”)

⁵⁴ See H.R. 1427, §3(a)(2), § 351(k)(11)(A) (where “[u]pon review of an abbreviated biological product application . . . for which a prior biological product has received a determination of interchangeability . . . , the Secretary shall not make a determination . . . that the *second or subsequent* biological product is interchangeable . . .”) See also H.R. 1548 §351(k)(6) (where “[t]he Secretary shall not make a determination under paragraph (4) that a *second or subsequent* biological product is interchangeable . . .”) [emphasis added].

⁵⁵ See 42 U.S.C. §262(k)(2), as amended, for a listing of required scientific information. BLA holders are obviously privy to their own trade secret and other proprietary manufacturing data. Under these circumstances, FDA may require little, if any, clinical trial data to grant interchangeability.

⁵⁶ Biogen received clinical trial data from Bioferon.

⁵⁷ Biogen held 50% equity in Bioferon allowing for an unrestricted flow of manufacturing data between the corporate entities.

⁵⁸ Based on total prescription sales as of November 11, 2013.

⁵⁹ On January 26, 2102, the US Court of Appeals for the Federal Circuit granted Amphastar a stay of the preliminary injunction preventing the marketing or selling of Amphastar’s generic enoxaparin. On the same day, Sanofi released a press statement that Winthrop U.S., LLC will again make it authorized generic version of LovenoxTM available in the USA “based on an assessment of market conditions.” For a very brief period beginning on November 30, 2011 and ending upon the entry of Amphastar into the generic enoxaparin market, Sanofi (via its Winthrop unit) temporarily discontinued marketing its AG-Lovenox.

⁶⁰ See 42 U.S.C. §262(k)(1) as amended (“*any* person may submit an application for licensure of a biological product . . .”) [emphasis added]. Interchangeable exclusivity only prevents a subsequent interchangeable product(s) from entering the market (i.e., biosimilars are not denied market entry). This conclusion assumes that the BLA holder is the first to gain marketing approval for an interchangeable.

of use . . .”⁶¹ While atypical from the current competitive follow-on biologic landscape, this example does highlight the likelihood that corporate collaborations will have advantages in rapidly manufacturing interchangeable versions of their own biologic products.⁶²

Reason 6: Third Party Payors and Physician Enlightenment

Due to the high cost of biological products, payors will likely encourage FDA approval of interchangeable biologics.⁶³ Payors have several options to dissuade use of the more expensive reference drug, including: (i) denying coverage to the reference biologic, (ii) requiring a higher co-payment for the reference biologic, (iii) requiring authorization for reference biologic and (iv) mandating “step therapy” where clinical failure of the cheaper interchangeable is a prerequisite to the more expensive reference biologic.⁶⁴ Even if FDA never officially allows a single interchangeable follow-on biologic, third-party payors and prescribers might create a *de facto* class of substitutable biologics.

Prescribing physicians often worry about unintended adverse immune responses when a patient is switched from a branded to a structurally dissimilar follow-on biologic. This prudent concern is only natural. With increasing clinical trial safety assurances⁶⁵, physicians will likely (albeit slowly) accept interchangeable biologics – especially for patients not previously administered a branded biologic.⁶⁶ For these drug naïve patients, it may be entirely possible that the interchangeable biologic is a better fit than the branded drug without concerns about cross-immunogenicity.

Lastly, due to the presence of immunologically active antigen-presenting cells in the skin (e.g., dendritic cells), physicians may be able to minimize risks of an adverse immune response by administering interchangeable follow-on biologics intravenously whenever possible.⁶⁷ Obviously, special care must be taken in administering follow-on biologics to patients with autoimmune disorders.⁶⁸

Reason 7: Post-Approval Biosimilar Data Accumulation

No less than fourteen non-interchangeable follow-on biologics are on the market in Europe.⁶⁹ European biosimilar applicants are requested to conduct post-approval pharmacovigilance studies for many follow-on biological products.⁷⁰ In the United Kingdom, follow-on biologic drug labels display a

⁶¹ See H.R. 1427, § 3(11), §351(k)(11). The term the term 'rebranded interchangeable biological product means “any rebranded interchangeable version of the reference product involved that the holder of the biological product license approved under subsection (a) for that reference product seeks to commence marketing, selling, or distributing, directly or indirectly . . .”

⁶² While statutorily defined “related entities” cannot receive additional 12 years market exclusivity for essentially, a follow-on biologic of one’s own BLA approved drug product gaining interchangeability exclusivity might run afoul of antitrust law.

⁶³ Payors include, for example, individual states (via Medicaid), formulary committees and prescribing physicians.

⁶⁴ See L. Loeb, *The Future of Biosimilars in the US: Legal, Regulatory, Scientific, Clinical and Payer Issues*, Drug Information Association, p. 14.

⁶⁵ Possibly from the generally positive European experience with non-interchangeable follow-on biologics.

⁶⁶ In this scenario, “interchangeability” is far less of an issue from an immune response perspective compared to patients previously exposed to a branded biologic. Here, a patient’s prescribed biological product is not being “changed”, rather initiated for the first time.

⁶⁷ See European Biopharmaceutical Enterprises, “Recommendations On The Use Of Biological Medicinal Products: Substitution And Related Healthcare Policies”, §3.3, January 2011, page 6. See also *Id.* Casadevall, N. (where a high correlation to adverse immune reactions was only observed in subcutaneous exposure, and not intravenous injection, of Eprex™ (epoetin alfa)).

⁶⁸ In particular, patients with a hyperactive IgE allergic response.

⁶⁹ Including the somatropin biosimilars Omnitrope™ and Valtropin™ based on branded Genotropin™ and Humatrope™, respectively; epoetin alfa biosimilars Binocrit™, Epoetin alfa Hexal™ and Abseamed™ based on branded Eprex™/Erypo™; epoetin zeta biosimilars Retacrit™ and Silapo™ based on branded Eprex™/Erypo™; filgrastim biosimilars Tevagrastim™, Ratiograstim™, Filgrastim Ratiopharm™, Biograstim™, Zarzio™, Filgrastim Hexal™ and Nivestim™ based on Neupogen™.

⁷⁰ Including the biosimilars for somatropin, interferon alpha, FSH, insulin, G-CSF, low molecular weight heparin and erythropoietin. For example, See “Guidance on Similar Medicinal Product Containing Somatropin”, Committee For Medicinal

black triangle symbol indicating that these products have been developed to be similar to an existing biological product. Inevitably, data will begin to accumulate suggesting that at least one European biosimilar is likely to be fully interchangeable with the reference product.

Several EMA guidelines additionally mention clinical pharmacokinetic crossover studies.⁷¹ In the United States, demonstration of interchangeability often requires some type of crossover or switchover clinical trial. Mentioned earlier, European approval of RetacritTM (an EprexTM/ErypoTM biosimilar) included Phase III crossover studies demonstrating near “identical” therapeutic equivalence.⁷² It seems reasonable to conclude that the accretion of European crossover studies will further facilitate interchangeable biologic approval by FDA.

Reason 8: Emergence of Follow-on Biologic Suitability Petitions?

Suitability petitions are traditionally relevant to the Hatch-Waxman generic drug approval process.⁷³ Here, a generic drug maker seeks to gain ANDA approval for a fully interchangeable generic drug despite being chemically distinct from the reference drug.⁷⁴ Indeed, non-identical, small-molecule ANDA drugs may be approved “because the new drug and the listed drug are produced or distributed by different manufacturers.”⁷⁵ While not a part of the PPACA, it does provide additional support for the claim that FDA is willing to allow interchangeability for non-identical drugs.

Interchangeable Follow-On Biologics: A Matter of Time

There has been much discussion about defining drug product attributes, or “goalposts”, for interchangeable follow-on biologics. While this is a good primary analogy, it is highly nuanced. Such a comparison may give the unintended impression that any approved interchangeable follow-on biologics was somehow held to a higher standard than its biosimilar counterpart. This may be misleading in certain situations when one considers that an individual interchangeable follow-on biologic was at one time “merely” biosimilar. Many biosimilar follow-on products are likely already interchangeable – we just don’t know it yet. Interchangeability cannot be analytically predicted – it can only be assured after extended use in humans. Put another way, an interchangeable is *the same* biological product as its biosimilar forerunner that has performed interchangeably in the real world.

The static goalpost analogy may also gloss over a possible temporal issue for the approval of interchangeable follow-on biologics. Unlike small molecule drugs, reference biological products are largely in a state of flux (e.g., “drift”) from the day they gain market approval to the day they are removed from the market. In a likely approval scenario, the follow-on biologic application will initially acquire

Products For Human Use (CHMP), 22 February 2006, page 5. EMEA/CHMP/BMWP/94528/2005. Notably, ZarzioTM was approved by the EMA based on four comparative PK/PD studies and a commitment to three Phase IV clinical safety studies. See “Fresh Insights Into the Practicalities of Developing Biosimilar Biologics”, Dowlat, H.A. 2009.

⁷¹ See for example EMEA/CHMP/BMWP/301636/2008 “Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant erythropoietins (Revision)”, European Medicines Agency, 18 March 2010 (“pharmacokinetic properties of the similar biological medicinal product and the reference product should be compared in single dose *crossover studies* . . .”). EMA guidelines for: G-CSF, heparin, interferon alpha and somatropin contain similar language.

⁷² *Id.* at p. 22 “[t]he course of the mean haemoglobin levels over time was practically identical for both products.” See also at p. 32 “the almost identical specific bioactivity of both products.”

⁷³ See FDCA §505(j)(2)(C).

⁷⁴ See 21 U.S.C. §355(j)(2)(C). Notably, FDA reserves the right to require studies “to show the safety and effectiveness of the drug or of any of its active ingredients, the route of administration, the dosage form, or strength which differ from the listed drug . . .” See also *Serono Laboratories, Inc. v. Shalala*, 974 F.Supp. 29 (D.D.C. 1997), 158 F.3d 1313 (D.C. Cir. 1998) (discussing FDA’s approval of a follow-on generic biologic menotropin product).

⁷⁵ See 21 C.F.R. § 314.127(a)(7). v12.

biosimilar status followed by significant patient use. Over time, encouraging real-world patient data will accumulate that supports a claim of interchangeability. Under this scenario, a more appropriate analogy may be a game of tennis where the ball represents the ever-in-motion drift of the biological product. The chalk lines represent the limits of acceptable analytic product attributes. The longer one keeps the ball (i.e., the biosimilar product) in the field of play (i.e., patient use) without any errors (i.e., serious adverse events) – the more likely it will gain interchangeability status. If so, gaining interchangeable follow-on biologic approval may just be a matter of time.

If you have any questions about this article, or would like to discuss this topic further, please feel free to contact:

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