Bioequivalence and Biosimilar Drug Development

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Introduction

This paper is a legal-philosophical analysis of the criteria and meaning of biological interchangeability in the context of biosimilar drugs and its implications for the practical aspects of biotechnological development.[1] Biologics can be used to treat human diseases or other health conditions from cancer to arthritis. Unlike chemical pharmaceuticals, biologics are isolated from a natural source and include "a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins." (FDA.gov) However, the prices of biologic drugs can be prohibitive. For instance, Roche's Herceptin® can cost $70,000 for one year of treatment. Non-name brand formulations are crucial for expanding access to pharmaceutical drugs. An innovator drug for a major disease may become commercially available, however it is likely to go to market at a high price, thus putting therapies out of reach for patients with limited financial resources or insurance. The Biologics Price Competition

[1] I do not claim to be an outright legal authority on the matters herein discussed, but rather hope to offer a thoughtful analysis of the issues presented in light of the letter of law. I ask the reader to excuse any important decisions or subtle interpretations that may have been overlooked.

and Innovation Act (BPCIA) provides a similar "abbreviated licensure pathway" for "biosimilar" or "interchangeable" biologic drugs, carving out an approval process for, and easier access to, biologic drugs. The similar 1984 Hatch-Waxman Act for chemical pharmaceuticals requires that a generic competitor demonstrate *bioequivalence*, defined as "[the absence of a] significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses." (FDA.gov) If a company can demonstrate biosimilarity, then it can take its biosimilar to market as a non-name brand product at a lower price. The FDA defines a biosimilar product as "a biological product that is approved based on a showing that it is highly similar to an FDA-approved biological product, known as a reference product, and has no clinically meaningful differences in terms of safety and effectiveness from the reference product," allowing only "minor differences in clinically active components" between the biosimilar and reference products. Further, the FDA defines "interchangeable biologic" as "biosimilar to an FDA-approved reference product [that] meets additional standards for interchangeability." Pharmacists can substitute interchangeable biologics for their reference product as chemical generics may be substituted, without worry of compromised safety or efficacy. (FDA.gov) Like Hatch-Waxman then, BPCIA, should improve access to biologic drugs.

Issue

Are the FDA criteria for biological interchangeability too narrow, and should they be broadened in order to stimulate development of, and consumer access to, biosimilars?

Parties

Party A – "Con": Chief Scientific Officer, Bristol Myers-Squibb (BMS)

Party B – "Pro": Director, Center for Biologics Evaluation and Research (CEBR)

Party A's Position on the Issue

Concise Statement of Party A's Position

No—broadening or loosening the definition will reduce the quality of available biologic drugs, put pressure on high performing drug companies, and increase the risk of pursuing cutting edge research programs.

Detailed Rationale for Party A's Position

Broadening the definition will reduce the quality of biosimilars, costing lives.

Unlike chemically synthesized pharmaceuticals, biologic products have an inherent amount of variability. While chemical pharmaceuticals are synthesized systematically atom by atom to produce copies of the same molecule, biologics are isolated from natural systems such as living cells and microorganisms that produce multiple copies of the same entity with subtle structural differences. Biologic products are thus significantly more complex than chemical products, and biosimilar pharmaceutical products should therefore be regulated strictly. The current criteria for biological interchangeability are necessary for ensuring a high standard of interchangeable biosimilar

quality. Broadening the definition of an interchangeable biologic will relax the evaluation and approval criteria for these products, opening he door to approving biosimilar drugs of lower quality than currently mandated. This puts the public at risk of receiving biosimilar products with inferior efficacy and safety. This will cost lives because these drugs can be substituted at the pharmacy level, unbeknownst to the patient and physician.

A broader definition will decrease motivation to develop innovator biologics.

If the definition or criteria for biological interchangeability are broadened, the wider scope will put pressure innovator biologics manufacturers. If creation and approval of an interchangeable biosimilar becomes easier, then smaller companies will wait for innovator companies to produce new biologics, then begin work on interchangeable biosimilars for those products. This sets up a competitive environment that undercuts the risk taken by innovator companies developing life saving biologics, especially after exclusivities expire, which will decrease motivation to develop innovator products. If innovator companies decrease their pace of research and development, or worse, abandon biologic research programs altogether as a result of this dynamic, lives will be lost to conditions that could be treated with biologic products. This situation can be avoided by keeping the high standard definition currently in place.

A broader definition will cost lives by increasing the risk of cutting-edge research.

Biologics have proven to be some of the most successful and powerful pharmaceutical products. This is partly due to the high degree of patent protection and extended exclusivity periods applicable to these products. Intellectual property rights and market exclusivity are two hugely

important factors in determining the risk of pursuing a particular avenue of research and development. In the case of biologics, the incentives have historically outweighed (or at least compensated) for the cost of undertaking research in uncharted areas of biomedical science. Post-patent and exclusivity protections are also important. If a broadened definition or criteria for biological interchangeability is introduced, it will cost lives because companies will exercise greater caution when entering a space allowing easier entry for competitors with a discounted product after exclusivities expire. If this market dynamic is enough to deter companies from entering the space, it will cost lives because research programs may be abandoned or not started.

Party B's Position on the Issue

Concise Statement of Party B's Position

Yes—broadening or loosening the definition will save lives by driving the prices of biologics down, test the viability of "interchangeability" as a condition for assessment, and drive innovation in the biosimilars industry by increasing competition.

Party B's Position and Rationale for why Party A's Position is More Compelling

Party B's position on the issue is that broadening or loosening the definition will save lives by driving the prices of biologics down, test the viability of "interchangeability" as a condition for assessment, and drive innovation in the biosimilars industry by increasing competition. Party B's position is tenuous because is fails to consider the impact of process engineering on the quality of biologic products. Since that are isolated form natural systems, biologic products are very sensitive

to production conditions. There is no guarantee that biosimilars manufacturing will produce the same quality product, with maintenance of efficacy and safety time. Even small environmental variabilities or fluctuations at biosimilar companies can produce an equally efficacious and safe, yet inferior biologic product. The assumed benefit to patients (i.e., reduced cost and increased access) may come at the price of lower quality products. If these products are substituted at the pharmacy, patients and physicians may not see the safety and efficacy over time they expect. With broadening the definition or criteria for biosimilar interchangeability comes the risk of producing inferior biologic products that may not maintain their efficacy over repeated administrations over a period of years. This is non-trivial, as patients receiving biologic therapy may need to be managed and treated regularly for decades, as in Crohn's disease or ulcerative colitis. These patients and their physicians need access to the highest quality biologic products available, so the criteria should not change.

Detailed Rationale for Party B's Position

<u>A broader definition will save lives by decreasing the prices of biologics.</u>

The prices of biologic drugs are prohibitive. For chronic diseases, years of treatment may thus cost patients hundreds of thousands of dollars. If a company can demonstrate that it has created a biosimilar biological product, then it can take this product to market in a manner similar to a generic drug, offering the product at a lower price than the innovator company, this will decrease prices of biologics and improve access to treatment with a biologically interchangeable, more affordable product. If the definition of biosimilar interchangeability is broadened, more companies will be willing to develop interchangeable biologics, and many patients who could previously not

afford biologic therapy will have access to affordable alternatives sooner than what is possible under the current law.

A broader definition creates an opportunity to evaluate the interchangeability criterion.

The requirements imposed by the definition of biosimilar interchangeability frustrate the feasibility of creating an interchangeable biosimilar. The act states that in order to be substituted, a biologic must be (1) biosimilar to its reference product, (2) can be expected to produce the same clinical result as the reference product in any given patient, and (3) must show no diminished safety or efficacy and no greater risk compared to the reference product over multiple administrations, or when alternating/switching with the reference product. Demonstration of (1) and (3) are reasonable, however (2) can be widened to increase activity in the biosimilars industry and evaluate the interchangeability criterion. Biological interchangeability as defined in (2) may be an impossible standard, and, there is no systematic way to determine of this criterion is practically feasible. Broadening the definition of biosimilar interchangeability will encourage more companies to develop these products and apply for interchangeable biosimilar approval, thus providing more information on which to evaluate the practicality of the current biosimilar interchangeability criteria.

A broader definition will spur competition in the biosimilars industry, saving lives.

Each patient is biologically different, and therefore may have a different reaction to a particular biologic due, for example, to immune system sensitivity. Accounting for these inevitable differences is non-trivial, and it is difficult to find the right data to support the assertion that an interchangeable biologic will act *identically* in *all patients* in *all situations*. In this sense, the law may be restrictive, creating

an insurmountable obstacle for biosimilar developers to overcome. If the criteria for biosimilar interchangeability is broadened, then applicants with interchangeable and biosimilar products will likely experience a higher probability of success in the approval process. Broadening the interchangeability requirements will lessen the pressure on these applicants to "prove the unprovable," increasing their willingness to take risks investing in interchangeable biosimilar programs. This will increase competition and drive innovation in the biosimilars industry, which will save lives by speeding up the development and availability of life-saving biologic drugs at affordable prices for patients.

Party A's Position and Rationale for Why Party B's Position is More Compelling

Party A's position is that broadening or loosening the definition of biosimilar interchangeability will reduce the quality of available biologic drugs, put pressure on high performing drug companies, and increase the risk of pursuing cutting edge research programs. Party A's argument that broadening the definition of will reduce the quality of biosimilars is confused, because Party B does not propose to relax the data requirements for biosimilar or interchangeable biosimilar approval, but wants to make it more feasible in theory to produce an interchangeable entity. CEBR will still to hold biosimilar applicants to a high standard, and scrutinize all the evidence we are provided to ensure that any candidate interchangeable biosimilar product is of the highest quality possible, as efficacious as the reference products, and substitutable with guaranteed efficacy and safety. Chemical drugs have been evaluated for decades under Hatch-Waxman and this experience can be adapted and evolved at CEBR to evaluate interchangeable biosimilars. Broadening the definition of biosimilar interchangeability will therefore not lessen the level of scrutiny exercised when evaluating applications. It will however encourage companies considering entering the

biosimilars space to do so. The current requirements seem unattainable on their face, and a more attainable requirement will spur more willingness and innovation, helping patients gain access to affordable biologics sooner. Further, experimenting with a broader definition of biosimilar interchangeability will save lives by helping test different and more efficient ways to evaluate interchangeable biosimilars.

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