Published on *The National Law Review* https://natlawreview.com

Generic Substitution and Biopharmaceuticals: Where Are All the Follow-on Biologics? And, How Much Money Will They Save?

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This article explores the viability of approving “follow-on” biologics (FOBs) and discusses how allowing an expedited process might reduce costs of these expensive biopharmaceuticals. First, it defines what is meant by the term “biopharmaceutical.” Second, it gives an overview of the science of biopharmaceuticals. Third, it reviews several practical issues surrounding FOBs. And, finally, it explores the potential economic impact of creating a new framework for expedited approval of follow-on biologics.

Introduction

A toy plane has a handful of parts. A Boeing 747 has several millions. This makes sense. Toy planes are small, simple models, while 747s are large, high-performance aircraft that travel more than 500 mph with thousands of component systems acting together. The toy costs a few dollars because it is easy to manufacture.[1] The 747 costs about $225 million because of its highly complex nature, testing and the need to ensure safety. This comparison is worth keeping in mind as the debate heats up on generic biopharmaceuticals.[2]

Single-source biopharmaceuticals have the potential to present important new pressures on the federal budget.[3] Congress has voiced concern over drug cost increases and is concerned with the possibility that competing low-cost substitutes to the brand-name biopharmaceuticals might not be available when the patents expire. As a result, several Bills have been introduced over the past three years that would create an expedited marketing approval pathway for “follow-on” biologics,[4] paving the road for a policy change that will someday allow for an easier process to approve these “follow-on” biologics (FOBs).

What are Biopharmaceuticals?

Biological products are proteins made by recombinant DNA technology. They function as a drug and are called many things, including biopharmaceuticals, biotech drugs, biological products or therapeutic biological products.[5] For the purpose of this article, we will refer to them as biopharmaceuticals.

The Public Health Services Act[6] defines term biological product as a product comprised of a biological product which is derived from and produced in living materials (such as microbial cells, mammalian cell lines, plant cell cultures, transgenic animals or plants)and "*are intended for use in the prevention, treatment or cure of a disease or condition in human beings*." [7]

This definition overlaps with the definition of a drug. The term "drug" includes "articles *intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals*."[8] As a result, biopharmaceuticals are regulated under the PHS and "drugs," which are regulated under the Food Drug & Cosmetic Act (FDCA).

The Science of Biopharmaceuticals

Many scientific disciplines contribute to biotechnology – molecular biology, microbiology, biochemistry, genetics, chemical engineering and cell biology.[9] The traditional medicines (often called "small molecule" drugs) which have historically been the mainstay of medical, nursing and pharmacy school education about drugs, are synthetic small molecules produced through chemical processes. They are discovered through high-throughput screens of tens of thousands of randomly generated compounds. On the other hand, biopharmaceuticals are macromolecules which are produce by living systems and created from amino acids and nucleic acids.

Biopharmaceuticals are generally much more complex than small-molecule drugs, and their manufacture often entails the use of live cells and complicated biologic processes.[10] The proteins are usually substantially large, complex molecules that may be mixtures of distinct entities.[11] For example, in Figure 1 (not included) we compare ibuprofen to erythropoietin. Ibuprofen's structure ($C_{13}H_{18}O_2$) is relatively simple and may be depicted with a simple diagram. It has a molecular weight of 206.28 Daltons and is synthesized chemically from isobutyl benzene.[12]

On the other hand, erythropoietin (EPO) a glycoprotein hormone (a cytokine) produced by recombinant DNA technology in mammalian cell culture. Its molecular description is much more complex.[13]

The process under which biopharmaceuticals are made is almost equally important to the structure of the drug. Even well-characterized, highly purified recombinant proteins may exhibit minor degrees of structural variability from lot to lot resulting from variations in the manufacturing process. The quality and nature of natural source products can vary depending on condition of the source material, processes used to extract and purify the product, and other factors.[14]

-Follow-On Biologics

Follow-on biologics (FOBs), also called biosimilars, biogenerics, biopharmaceuticals, follow-on proteins or biocomparable proteins,[15] may be a way to greatly reduce rising drug prices. The term FOB generally refers to protein and peptide products that are intended to be similar enough to an already approved biopharmaceutical so that the follow-on manufacturer can rely on certain existing scientific knowledge about the safety and effectiveness of the biopharmaceutical.[16]

Given the large costs associated with the development and clinical testing of a biopharmaceutical, the manufacturer of such a product almost always will obtain patent protection for the product before investing in testing and the FDA approval process. Because of the long approval process, most manufacturers will have only 7-12 years of market exclusivity provided by the patient. Once the

patent expires, other manufactures would conceivably be free to seek approval to manufacture the product. Some biopharmaceutical patents have already expired. A number of others are due to expire in the next few years.[17]

However, the potential opportunity for price reductions versus the originator biopharmaceuticals remains to be determined, as the advantage of a slightly cheaper price may be outweighed by the hypothetical increased risk of side-effects from FOBs that are not exact copies of the originator protein.[18]

FDA Approval of FOBs

All drugs and biopharmaceuticals must have either a new drug application (NDA) or a Biologics License Application (BLA) approved by the FDA before they may be marketed in the United States.[19] Prior to 1984, generic drug manufacturers would need to file a complete NDA before marketing their products, making it a difficult, cumbersome and expensive process to bring a generic to market. [20]

In an effort to make it simpler for generic products to be introduced into the market, two alternative shorter processes were created by the Drug Price Competition and Patent Term Restoration Act (the Hatch-Waxman Act).[21] Section 505(j)[22] created the abbreviated new drug application (aNDA) process. Using the aNDA process, a generic manufacturer seeking to market a product having the same active ingredient, route of administration, dosage form and strength as the brand-name drug may rely on the safety information from the original manufacturer. This allows for generic companies to seek approval by showing bioequivalence prior to the innovator's patent expiring, so that the generic drug can be available on the day the patent expires.[23]

A second abbreviated process exists for products that do not have the same active ingredient, route of administration, dosage form or strength. Under Section 502(b) (2),[24] drugs that either differ from an approved innovator product or require additional human studies for approval may rely upon safety and efficacy studies performed by others such as the original manufacturer.

As discussed above, biopharmaceuticals are considered to be "drugs."[25] Therefore, theoretically this second pathway could apply to biopharmaceuticals allowing a shortened approval process for follow-on biologics. However, the FDA has only applied 505(b)(2) pathway to those biopharmaceuticals which have been regulated as drugs under the FDCA, such as human growth hormone, [26] taking the position that additional legislation is required to provide such a pathway for those biopharmaceuticals that are licensed as "biologics" under the PHS Act.[27]

Generic Substitution

After the FDA approves a generic, the question of whether it is generically substitutable is a matter of state law. Generally, a drug may be generically substituted when it: (1) has the identical amount of the same active chemical ingredients; (2) is in the same dosage form; (3) meets applicable standards of strength, quality and purity according to a nationally recognized compendium; and (4) if administered in the same amounts, will provide comparable therapeutic effects.[28] The states differ on how they determine which products are "generically equivalent." Some states have a "positive formulary" which lists all of the products which may be generically substituted in that state.[29] Others have a "negative formulary"[30] which lists those drugs – generally narrow therapeutic index (NTI) drugs[31] – that may not be substituted. And, others default to the FDA's

determination of whether the product is bioequivalent.[32]

For those states that allow generic substitution according to the FDA's determination of bioequivalency, pharmacists must consult the FDA's publication entitled *Approved Drug Products with Therapeutic Equivalence Evaluations* (commonly known as the Orange Book).[33]

In addition, the List contains therapeutic equivalence evaluations for approved multisource prescription drug products. In general, drugs that are "A" or "AB" rated are generically substitutable.[34]

Difficulty with Generic Biopharmaceuticals

Because it will difficult to show bioequivalency, biopharmaceuticals will most likely not be A or AB rated. Therefore, pharmacists will not be able to automatically generically substitute similar products. With small molecular products, there is a long history to support the use of various scientific approaches to establishing bioequivalence between products with the same active ingredient(s) produced by different manufacturers. [35] We know now that these bioequivalent[36] products can generally be expected to behave in a pharmacologically interchangeable manner when used in patient care. [37] With biopharmaceuticals, the FDA has not determined how interchangeability can be established for complex proteins.[38]

Because of the variability and complexity of protein molecules, the FDA believes that current limitations of analytical methods, and the difficulties in manufacturing a consistent product, make it unlikely that, for most biopharmaceuticals, a manufacturer of a follow-on protein product could demonstrate that its product is identical to an already approved product.[39] This is because while the patent lists the ingredients, the manufacturing process for the product is likely protected as a trade secret.[40]

One alternative is to use the safety and effectiveness data of an already-approved biopharmaceutical. This could be done by extending the 505(b)(2) process to all biopharmaceuticals, including those that have been issued a BLA. However, demonstrating the similarity of a follow-on biologic is more complex and requires more new data than is needed to determine whether a manufacturing change will affect the product.[41]

In general, the required new data will be influenced by the extent to which the FOB can be demonstrated to be sufficiently similar (structurally, functionally, and clinically) to an approved protein product to permit some degree of reliance on the findings of safety and effectiveness for the approved product.[42] In addition, the amount and type of new data needed will be influenced by the clinical use of the product and the amount and type of clinical experience that has been accumulated about the approved product as well as related products.[43]

Current technologies, such as peptide mapping, protein sequencing, and mass spectroscopy enable manufacturers to determine, with certainty, the amino acid sequence of a recombinant protein. However, the amino acid sequence is the most rudimentary characteristic of a protein – making the current method of evaluating equivalence fraught with uncertainties.[44] Thus, predicting the clinical comparability of two products depends on our understanding of the relationship between the structural characteristics of the protein and its function, as well as on our ability to demonstrate structural similarity between the follow-on protein and the reference product.[45]

The most critical safety concern relating to biopharmaceuticals is immunogenicity.[46] All biopharmaceuticals are biologically active molecules derived from living cells, and have the potential to evoke an immune response. Although the immunogenic potential cannot be predicted through chemical or structural analyses of the biopharmaceutical, several factors are known to affect a product's immunogenic potential. The presence of impurities in the final product, structural modifications as a result of the manufacturing process and/or storage conditions can increase immunogenicity.[47]

How Much Money Will Follow-On Biologics Save?

Will FOBs be cheaper than the originals? To some degree that depends on Congress and whether a resulting law requires limited or extensive clinical trials. Even if Congress passes a bill creating a method to approve FOBs, the follow-ons most likely will not be generically substitutable. A finding of safety and efficacy is distinct from determining that the FOB would be substitutable (*e.g.,* A or AB-rated) for the innovator biopharmaceutical.

In addition to not being generically substitutable, a follow-on manufacturer would need to engage in additional tests to demonstrate that the two products would be therapeutically substitutable. This would requiring showing that switches between the products would not negatively affect the safety or effectiveness of the products as a result of immunogenicity. For many follow-on protein products -- and in particular, the more complex proteins – repeated switches between products may negatively impact safety or effectiveness. Therefore, the ability to make determinations of substitutability for follow-on protein products may be limited.[48]

Protein drugs require living cells and a delicate and very expensive manufacturing process that pushes the cost of developing a new drug, even a look-alike, to $200 million to $300 million- that is less than the average $900 million you need to launch an original drug.[49] But it is much more than what it costs to copy a simple molecule like the one in Zocor or Zantac.

It is unclear how much developing a FOB abbreviated pathway will yield. One recent study estimated a savings over a 10-year period of approximately $71 billion.[50] Another study estimated that Medicare Part B (which pays for drugs such as chemotherapy which are administered at a physician's office) could save approximately $14 billion from 2007-2017.[51] Another study estimated savings would be only $3.6 billion over the next 10 years.[52]

Critics have said that these estimates may be overstated,[53] because of the more expensive manufacturing process than small molecule drugs[54] and the need for the follow-on manufacturer to engage in costly marketing including hiring salespeople to educate the prescribers about the interchangeability.[55] Because FOBs will most likely not be A or AB-rated generics, making them similar to narrow therapeutic index drugs, pharmacists will need to contact physicians for a new prescription if a patient requests – or their health plan encourages – that the FOB be dispensed. Although a FOB may prove to be as safe as the originator product, switching the patient between products will need to be handled with caution.[56] Manufacturers, physicians and pharmacists will need to provide information to patients and their caregivers so that they can assess the risks involved in switching from an established product to a follow-on biologic.[57]

Further, biopharmaceuticals tend to have smaller target markets for which incentives to entry may not be as high, and they tend to be used to treat life-threatening diseases, for which managed care organizations are often less likely to utilize price control measures.[58] As a result, some

economists argue that very few FOB companies are likely to emerge, making price drops for consumers unlikely to utilize price control measures.[59] Historically, when there are only a small number of generic drugs available, prices generally don't go down very much. For example, the average price reduction for a generic that has been granted 180-day exclusivity[60] is only 30%, as compared to a 70% amount for multi-source generics[61].

On example of disappointing discounts is Omnitrope, a biosimilar version of Pfizer's human growth hormone (HGH) Genotropin. Omnitrope was launched under special rules in Europe and the U.S. several years ago by Novartis' Sandoz subsidiary. The first biosimilar to reach patients in the developed world, it has captured less than one percent of the $831 million European HGH market. Aitken attributes this performance to the conservatism of doctors, as well as issues around its delivery mechanism. Also, the price is only 20-25 percent below that of the patented version as opposed to 50-70 percent below for traditional generic medications.[62]

However, even if savings from FOBs turn out to be far less than some predictions, there are a lot of people for whom the savings are important, such as legislators who are struggling with the deficit and the increase in federal health care program costs, as well as patients.[63] It will be interesting to watch the evolution of follow-on biologics, how they will improve patient care, decrease overall drug spend and help the world.

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[1] Bryan Liang, Don't Compromise the Safety of Biotech Drugs, LA Times (6/28/08).

[2] *Id.*

[3] Richard G. Frank and Joseph P. Newhouse, *Should Drug Prices Be Negotiated Under Part D Of Medicare? And If So, How?*, Health Affairs 27, no. 1 (2008): 33-43 January, 2008 - February, 2008

[4] The "Promoting Innovation and Access to Life Saving Medicines Act" (H.R. 1427) was introduced March 11, 2009 and sponsored by Rep. Henry Waxman (D-CA) and companion bill S.B. 726, introduced March 26, 2009 and sponsored by Sen. Charles Schumer (D-NY); the "Pathway for Biosimilars Act (H.R. 1548) was introduced March 17, 2009 and sponsored by Rep Anna.Eshoo (D-CA). In addition, at least three bills were introduced in 2007 and 2008: the "Access to Life-Saving Medicine Act" (H.R. 1038 and S. 623) ; the "Affordable Biologics for Consumers Act" (S. 1505 and HR. 3496); and "Biologics Price Competition and Innovation Act of 2007" (S. 1695) would proscribe how products could be interchangeable.

[5] Rader, R., What is a Generic Biopharmaceutical? Biogeneric? Follow-on Protein? Biosimilar? Follow-on Biologic? Bioprocess International, May 2007 at p. 20.

[6] The term "biological product" means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings. *42 USC 262(i) (Sept. 27, 2007).*

[7] 21 CFR § 600.3(h).

[8] 21 USC § 321(g)(1)(B).

[9]Grace ES. *Biotechnology Unzipped. Promises and Realities*. 2nd edition. 2006.

[10] Frank, R., *Regulation of Follow-on Biologics*, N.Engl.J.Med. 357:9 (Aug. 30, 2007) at page 842

[11] Statement of Janet Woodcock, M.D., before the U.S. House of Representatives Committee on Oversight and Government Reform (Mar. 26, 2007) (**hereinafter, "Woodcock Statement"**).

[12] Remington's Pharmaceutical Sciences, 17th Ed. (1985), p. 1117.

[13] RCSC Protein Data Bank, available at: http://www.rcsb.org/pdb/explore/explore.do?pdbId=1jpp

[14] Woodcock Statement.

[15] Rader, R., What is a Generic Biopharmaceutical? Biogeneric? Follow-on Protein? Biosimilar? Follow-on Biologic?, BioProcess International (May 2007), at 20.

[16] Omnitrope (somatropin [rDNA origin]) Questions and Answers, available at: http://www.fda.gov/cder/drug/infopage/somatropin/qa.htm

[17] Roger, S. and Mikhail, A., *Biosimilars: Opportunity of Cause for Concern?*, J. Pharm Pharmaceut Sci 10(3): 405-410 (5/18/07).

[18] Id.

[19] 505 of FDCA, 351 of PHS.

[20] Gerald J. Mossinghoff, Overview of the Hatch- Waxman Act and Its Impact on the Drug Development Process, 54 Food & Drug L.J. 187 (1999)

[21] PL 98-417 (S 1538) September 24, 1984

[22] 21 USC § 355(j)(1) (2004).

[23] 1999 Guidance on 505(b)(2)

[24] 21 U.S.C. § 355(b)(2) (2004).

[25] See note 15, supra.

[26] In fact, this method has been used by several manufacturers to approve certain FOBs such as recombinant Hylenex® (hyaluronidase recombinant human), Hydase® and Amphadase® (hyaluronidase), and Fortical® (calcitonin salmon recombinant) Nasal Spray, GlucaGen® (recombinant human glucagon), and human growth hormone (Omnitrope® and Valtropin®). *See*, Omnitrope (somatropin [rDNA origin]) Questions and Answers, available at http://www.fda.gov/cder/drug/infopage/somatropin/qa.htm

and "Stealth" Follow-on Protein Approval by FDA?, retrospective commentary on Generic BIOPHARMA website: http://www.followonproteins.com/

[27] Johnson, J., CRS Report for Congress: FDA Regulation of Follow-On Biologics (Aug. 6, 2007), page CRS-7.

[28] See, e.g., Ala. Code §34-23-8(1); Ar. Rev. Stat. § 32-1963.01.

[29] See, e.g., D.C. Code Ann. §§ 33-731, 33-733.

[30] See, e.g., Fla. Stat. 465.025.

[31] A list of so called narrow therapeutic index drugs was prepared by the Center for Drug Evaluation and Research in order to assist the FDA District Offices in their testing program that came about because of problems with the generic industry in the late 1980's. This working list of drugs is also currently being used as one of the factors to determine if an in vivo study or other data are needed to determine the impact of post-approval changes in the manufacture of a drug product. The list is in the "Scale-Up and Post-Approval Changes for Intermediate Release Products" (SUPAC-IR),"

available at: http://www.fda.gov/cder/guidance/cmc5.pdf

[32] See, e.g., Haw. Rev. Stat. § 328-92.

[33]The Electronic Orange Book is accessible online at: http://www.fda.gov/cder/ob/default.htm. The Orange Book identifies approved drug products except for those drugs covered by the ongoing Drug Efficacy Study Implementation (DESI) review (e.g., Donnatal®Tablets and Librax® Capsules) or pre-1938 drugs (e.g., Phenobarbital Tablets).

[34] "A" rated products are those drugs that are considered to be therapeutically equivalent to other pharmaceutically equivalent products in the Orange Book. "A" rated products are designated AA, AN, AO, AP or AT, depending on the dosage form. "AB" rated products are those drugs that the FDA considers to be therapeutically equivalent to other pharmaceutically equivalent products when actual or potential bioequivalence problems have been resolved with adequate *in vivo* or *in vitro* evidence supporting bioequivalence.

[35] U.S. FDA Considerations: Discussion by National Regulatory Authorities with World Health Organization (WHO) On Possible International Non-proprietary Name (INN) Policies for Biosimilars (September 1, 2006), available at: http://www.fda.gov/cder/news/biosimilars.htm

. **(Hereinafter, "U.S. FDA Considerations").**

[36] The FDA defines "Bioequivalent Drug Products" as "pharmaceutical equivalent or pharmaceutical alternative products that display comparable bioavailability when studied under similar experimental conditions. "Bioavailability" means "the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action." 25th Edition ORANGE BOOK, pp. vii - viii.

[37] U.S. FDA Considerations.

[38] *Id.*

[39] Woodcock Testimony.

[40] Bruce S. Manheim, Jr. Patricia Granahan, Kenneth J. Dow, "*Follow-On Biologics: Ensuring Continued Innovation in the Biotechnology Industry*," Health Affairs (March- April 2006) 25, no. 2 (2006): 394-404 at 397.

[41] Woodcock Testimony.

[42] *Id.*

[43] Id.

[44] Id.

[45] Id.

[46] H. Schellekens, Biosimilars: Opportunity or Cause for Concern? Citing H. Schellekens. Bioequivalence and the immunogenicity of biopharmaceuticals, Nat Rev Drug Discov, 1:457-462, 2002. M. Kessler, D. Goldsmith, and H. Schellekens, Biosimilar therapeutic agents: issues with bioequivalence and immunogenicity, Eur J Clin Invest, 34:797-799, 2004. H. Schellekens and N. Casadevall, Immunogenicity of biopharmaceuticals, Nephrol Dial Transplant, 21 Suppl 5:v8-v12, 2006.

[47] Biosimilars: Opportunity or Cause for Concern?, Note 37.

[48] Woodcock Testimony.

[49] **Needle Work, (Forbes)** Matthew Harper 03.10.08

[50] Miller, S. & Houts, J. *Potential Savings of Biogenerics in the United States*, (Feb. 2007), available at http://www.express-scripts.com/industryresearch/outcomes/onlinepublications/study/potentialSavingsBiogenericsUS.pdf

. The analysis was based on prescription drug use for two samples of three million unique Express Scripts customers in 2005 and 2006 (the ESI Study)

[51] Engel & Novitt, Potential Savings That Might Be Realized By the Medicare Program from Enactment of Legislation Such As the Access to Life-Saving Medicine Act (H.R. 6257/S. 401B) that Establishes a New cBLA Pathway for Follow-On Biologics, (the "PCMA Study")

[52] Avalere Health, LLC study (cited in PhRMA statement on FOBs)

[53] A February 2007 article authored by the Director of Economic Policy for the Biotechnology Industry Organization, the trade group for innovator biopharmaceutical manufacturers, identified nine analytical flaws in the ESI Study and the PCMA Study, chief among them being a presumption that a FOB pathway would generate the same savings as generic drugs, market penetration rates for FOBs, assumptions about patent expiration, calculation errors in the PCMA study, internally inconsistent allegations of interchangeability in the ESI study, and calculations based on unsupported

determinations of interchangeability. Ted Buckley, "Recent Studies on Follow-On Biologics are Based on Seriously Flawed Assumptions," (Feb. 22, 2007: available at http://www.bio.org/news/newsitem.asp?id=2007_0222_06

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[54] Schacht, FOBs, at CRS-21.

[55] Schacht, FOBs, at CRS-23.

[56] Biosimilars: Opportunity or Cause for Concern?, Note 37 at p. 408.

[57] Biosimilars: Opportunity or Cause for Concern?, Note 37 at p. xxx

[58] Kathleen R. Kelleher, *FDA Approval of Generic Biologics: Finding a Regulatory Pathway*, 14 Mich. Telecomm. & Tech.L Rev 245 (2007), available at http://www.mttlr.org/volfourteen/kelleher.pdf

, citing, Stephan Herrera, *Biogenerics Standoff*, 22 Nature Biotechnology, 1343, 1345 (Nov. 2004).

[59] id.

[60] Generics manufacturers are rewarded for successfully challenging a patent: the first firm that files an Abbreviated New Drug Application is granted 180-day products. Richard G. Frank, Ph.D., *The Ongoing Regulation of Generic Drugs*, N.Eng.J.Med Volume 357:1993-1996 November 15, 2007 Number 20.period of exclusive marketing among generic

[61] Michelle L. Kirsche, "As brand-generic alliances grow, opponents cry foul," Drug Store News, August 23, 2004.

[62] IMS Health: *Biosimilars: How Strong a Market?*, Sep 4, 2007,available at: http://www.imshealth.com/ims/portal/front/article/CIS-27777,00/68_5368_82387735,00.html

[63] Lisa Layman (Gen. Pharm. Assn, Assoc. VP of Govt. Aff. & Policy, quoted in FDA Legislative Watch (04/01/08) "Potential Federal Drug savings Could Propel Biosimilars Bill," available at: http://www.biotechnologyresearch.com/2008/04/potential-feder.htm.

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