

IT'S THE ANTIGEN STUPID¹: A RISK/REWARD APPROACH TO THE PROBLEM OF ORPHAN DRUG ACT EXCLUSIVITY FOR MONOCLONAL ANTIBODY THERAPEUTICS

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The Orphan Drug Act of 1983 is an attempt at solving an important problem: how to induce a market-driven pharmaceutical industry to develop new therapeutics for diseases affecting relatively small numbers of persons. In the case of protein therapeutics produced by biotechnology, the FDA's administration of the Act has repeatedly led to litigation and controversy. The principal and recurrent problem has been determining when a second applicant for the approval of a drug to treat an orphan disease (or "indication") is seeking approval for the "same" drug as a previously approved orphan drug. The problem is how to provide sufficient protection for pioneering orphan drugs to stimulate the development of new drugs for smaller patient populations, while not so broadly protecting orphan drugs as to preclude additional therapeutics that make new contributions to the treatment of those diseases. In the context of antibody therapeutics, that problem is somewhat different than for other protein therapeutics. For antibodies, it is the antigen that will primarily determine the antibody's efficacy, and it is the proof that an antigen is clinically useful in the treatment of a disease that provides the biggest risk in antibody development. The approach to orphan drug exclusivity recommended here is that the FDA presume antibodies to the same antigen, of the same immunoglobulin class and with the same mechanism of action to be the same drug unless the second antibody is shown to be clinically superior to the first.

¹ "It's the Economy Stupid" was the central theme of Bill Clinton's 1992 run for the presidency. It is used here as a reminder that a successful approach to important problems requires keeping a clear focus on the central issue. See David S. Broder and Dan Balz, *Gore Fails to Cash In on Prosperity; Swing Voters Give Vice President Little Economic Credit*, Wash. Post, July 23, 2000, at Section A, page A01 for a reference to the Clinton theme.

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I. Introduction

The Orphan Drug Act of 1983 (the “Act”)² is an attempt at solving an important problem: how to induce a market-driven pharmaceutical industry to develop new therapeutics for diseases affecting relatively small numbers of persons. Although some drugs for small patient populations have been exceedingly profitable,³ the need for special incentives to spur pharmaceutical manufacturers to undertake the costly and risky process of drug development and research for less common diseases was clear to the Congressional sponsors of the Act and the Act has been largely judged a success.⁴ A key part of the solution that the Act provides is to reward manufacturer “sponsors” of orphan drugs with a seven year period of market exclusivity, during which the FDA will approve no other application to treat the same disease with the same orphan drug. An orphan drug is defined as one treating a disease or condition which affects less than 200,000 persons in the United States or affects more than 200,000 persons but for which there is “no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug.”⁵

² Pub. L. No. 97-414, 96 Stat. 2049 (1983) (codified as amended in scattered sections of 21 U.S.C. and 42 U.S.C.). See also Orphan Drug Regulations, 56 Fed. Reg. 3338, 3338 (1991) (to be codified at 21 C.F.R. pt. 316) (proposed Jan. 24, 1991) (discussing legislative intent to provide economic incentives) (hereinafter “Proposed Regulations”). This Article is specifically about the problem of monoclonal antibodies under the Orphan Drug Act and is not intended to be a complete introduction to the Orphan Drug Act and its applications. Those interested in an expanded introduction to the Act and its history should see Robert A. Bohrer & John T. Prince, *A Tale of Two Proteins: The FDA’s Uncertain Administration of the Orphan Drug Act*, 12 Harv. J.L. & Tech. 365 (1999) (arguing that the FDA’s approach to determining orphan drug sameness for protein therapeutics is overly generous to second applicants for orphan drug approval) (hereinafter “Bohrer & Prince”); see also David B. Clissold, *Prescription for the Orphan Drug Act: The Impact of the FDA’s 1992 Regulations and the Latest Congressional Proposals for Reform*, 50 Food & Drug L.J. 125 (1995) (providing an analysis of the U.S. Orphan Drug Act and proposed legislative changes to it); see also Gina M. Cavalier, Note, *Pushing Parentless Pharmaceuticals: Toward an International Home for “Orphan Drugs” and a Cure for “Zebra” Diseases*, 27 Law & Pol’y Int’l Bus. 447 (1996) (providing a general overview of orphan drug development in the U.S. and Japan, as well as recommendations for an EU orphan drug policy).

³ For example, Genzyme’s Ceredase® is a therapeutic for Gaucher’s disease, which afflicts approximately 20,000 persons in the United States. The only treatment for that very serious disease, Ceredase® costs patients an average of \$145,000 per year, providing Genzyme with revenues of \$172 million in 1994. Alex Pham, *Ceredase® Report May Foretell Trouble for Genzyme*, Boston Globe, Mar. 2, 1995, at 36. The problem of the high cost of orphan drugs is an important one, but is beyond the scope of this paper. So long as market exclusivity and profits remain the principal incentive for drug discovery and development, the problem of drug cost and access to important therapeutics will be a problem that needs to be addressed. However, since market exclusivity is in fact a principal incentive provided in the Orphan Drug Act, the purpose of this paper is to critique the FDA’s administration of that incentive in its own terms.

⁴ Abbey S. Meyers, *Intellectual Property at the Public-Private Divide: A Response*, 3 U. Chi. L. Sch. Roundtable 581 (1996) (attributing the success of the Orphan Drug Act to its exclusivity incentives while questioning the need for broad patents on gene sequences).

⁵ 21 U.S.C. § 360ee(b)2 (2000).

Despite the apparent simplicity and straightforward logic of the Act's solution to the orphan disease problem, the FDA's administration of the Act has repeatedly led to litigation and controversy.⁶ The principal and recurrent problem has been determining when a second applicant for the approval of a drug to treat an orphan disease (or "indication") is seeking approval for the "same" drug as a previously approved orphan drug. The FDA's original approach to the "same drug" problem was to permit any chemical difference between a first and second orphan drug to be sufficient for the second to be approved. This chemical identity test clearly undermined the basic purposes of the Act when applied to protein therapeutics. In the new era of biotechnology, it proved all too easy for pharmaceutical manufacturers to make changes in a pioneering drug that would not affect its biological activity, and, if approved as a second entrant for an orphan indication, would greatly diminish the value of Orphan Drug Act exclusivity.⁷ The FDA has recognized the problem and repeatedly grappled with it.⁸

More recently, the FDA has revisited the problem of distinguishing same versus different under the Act for monoclonal antibody-based drugs, which are an important category of biotechnology-derived therapeutics. Once again, the FDA appears to have gotten it wrong, providing a "solution" to the same versus different problem that seems almost certain to engender further uncertainty and litigation, and to undermine the important exclusivity incentives of the Act. I use the word "problem" throughout this Article to refer to difficulty in determining the appropriate means by which to accomplish particular objectives.⁹ In the case at hand, orphan drugs, the objective is to provide sufficient protection for pioneering orphan drugs to stimulate the development of new drugs for smaller patient populations, while not so broadly protecting orphan drugs as to preclude additional therapeutics which make new contributions to the treatment of those diseases. In other words, the problem is to distinguish truly "different" second entries into orphan drug markets from would-be competitors that are more or less the "same" as the innovator first-entrant.

⁶ See *Berlex Labs v. FDA*, 942 F. Supp. 19 (D.D.C.1996); *Genentech, Inc. v. Bowen*, 676 F. Supp. 301, 306 (D.D.C. 1987); Bohrer & Prince, *supra* note 2.

⁷ *Berlex Labs*, 942 F. Supp. at 23.

⁸ See *The Pink Sheet*, Vol. 60; No. 19; Pg. 19 May 11, 1998:

FDA is planning to update its definitions of orphan drug "sameness" and "difference" to address new issues related to biotechnology and biologics, FDA Office of Orphan Products Development Director Marlene Haffner said at a May 5 workshop in Brussels on rare diseases and orphan drugs.

"Same versus different keeps challenging us," Haffner stated at the meeting, which was sponsored by the European Foundation for the Advancement of Science. "We just discovered some holes in our regulation that we didn't know about even last year, so we are going to be republishing some questions."

⁹ See generally Thomas D. Barton, *Creative Problem Solving: Purpose, Meaning, and Values*, 34 Cal. W. L. Rev. 273 (1998). Barton views problems as a disjuncture between environment and desired objectives, with problem solving being an effort to get from the initial environment to the desired objective. Here the problem is providing adequate incentives and certainty for the developers of antibodies for orphan diseases.

A reasonable solution to the problem of orphan drug “sameness,” for monoclonal antibodies as well as other therapeutics, should satisfy three criteria. First, it must not undermine the essential incentives of the Orphan Drug Act for undertaking the risky process of drug development for small patient populations. Second, the criteria for determining sameness must provide relatively clear guidance to pioneer orphan drug developers as to the probable scope of their protection, at the earliest possible stages of drug development. Finally, the criteria must also provide would-be second entrants relatively clear guidance as to their chances of successful approval by the FDA as “different” and a reasonably clear roadmap to the approval of a second orphan antibody for the same indication. The FDA’s efforts, which have focused on the chemical composition of monoclonal antibody therapeutics, have not been particularly successful at addressing these concerns, both with respect to not undermining the Act’s incentives and in providing clear guidance to pioneer orphan drug developers and second entrants.¹⁰

This Article will take a very different approach than that of the FDA to solving the problem of Orphan Drug Act exclusivity for monoclonal antibody products, one that attempts to relate orphan drug exclusivity rewards to the degree of orphan drug sponsor risk. In providing the basic incentive of exclusivity, the Orphan Drug Act sponsors clearly intended to provide a sufficient reward for undergoing the risky (and costly) process of drug development. Therefore, this Article suggests that by focusing on the factors that determine the degree of risk in orphan drug development, the FDA can implement guidelines for monoclonal antibodies that better serve the purposes of the Act and solve the “same drug” problem in a much more satisfactory manner. In other words, if the purpose of orphan drug incentives is to provide incentives for risky, expensive drug development, then orphan drug protection (and its converse, second-entry approval) should be correlated with the degree of risk faced by the applicant. To use an example from a non-orphan drug context, the first developer of a selective serotonin reuptake inhibitor (Prozac®) faced a good deal more uncertainty over the likelihood of proving efficacy in the clinic than subsequent developers of drugs in that class. Second entrants into a therapeutic class still face risk and may make important contributions (in increased efficacy or a better side effect profile) but do not face the same level of risk as the pioneer entrant.

Antibody therapeutics can be similarly thought of as belonging to therapeutic classes, in which the pioneer entrant faces the greatest risk. In particular, I will argue that the biggest risk-creating uncertainty in developing a monoclonal antibody therapeutic for the treatment of a disease (orphan or otherwise) is whether an antibody directed to the particular disease-related target (antigen, in antibody terms) will prove to have a sufficient positive therapeutic effect. In other words, at the present state of antibody science, the biggest unknown is the value of the antigen selected as a target for particular disease. Thus I will propose regulations under which the FDA would require sponsors of

¹⁰ Draft Guidance for Industry - Interpreting Sameness of Monoclonal Antibody Products Under the Orphan Drug Regulations, <http://www.fda.gov/cber/gdlns/orphan.htm> (hereinafter “Guidance”) (last visited April 23, 2003).

second antibody therapeutics aimed at the same antigen target for the same disease to demonstrate the clinical superiority¹¹ of their antibody.

Part II of this Article provides a brief background to the field of monoclonal antibodies and the development of monoclonal antibodies as therapeutics. Part III reviews the history of the FDA's interpretation of the Orphan Drug Act and the FDA's recent "Guidance for Industry: Interpreting Sameness of Monoclonal Antibody Products Under the Orphan Drug Regulations."¹² Part IV provides the proposed framework for evaluating solutions to the problem of sameness for monoclonal antibody products—a risk-reduction-based model which rewards risk-taking pioneer orphan antibody developers by grounding orphan drug exclusivity in the magnitude of the risk faced by competing orphan drug sponsors for the same indication. In Part V, the Article concludes with a summary of the proposed antigen-based framework for determining the sameness of antibody products in terms of the risk-reduction criteria of Part IV.

II. An Introduction to Monoclonal Antibodies

Antibodies are proteins¹³ made by the B cells of the immune systems of higher organisms (see Figure 1 for a detailed drawing of a typical antibody, or an Immunoglobulin G or "IgG"). The function of an antibody is to bind to an antigen, or substance which is recognized by the immune system as "foreign" and which therefore stimulates an immune response. A three-dimensional feature of an antigen to which an antibody can bind is called an antigenic determinant, or epitope. Large antigens can have many epitopes and even a single epitope may be the target for a number of different antibodies.¹⁴ Thus, stimulation of the immune system by a pathogen, such as a virus, results in many different B cells producing antibodies to that pathogen.

¹¹ Clinical superiority is a concept currently employed by the FDA to allow sponsors of second orphan drugs that are substantially similar to first-approved orphan drugs to nevertheless gain approval. *See Berlex Labs*, 942 F. Supp. at 19. Clinical superiority is determined by greater effectiveness or fewer side effects or, in some cases, by greater patient ease-of-use, such as an oral form instead of an injectable one. *See* 21 C.F.R. 316.3 (b)(13) *et. seq.*

¹² *See* Guidance, *supra* note 10.

¹³ Proteins, which may also be referred to as polypeptides, are long chains of amino acids, joined together by what chemists refer to as a peptide bond. Proteins may also have carbohydrate, or sugar, molecules attached to one or more of the amino acids of the protein. Such sugar-coated proteins are known as glycoproteins. *See* Bruce Alberts et al., *The Molecular Biology of the Cell*, 107, 417 (2d ed. 1989).

¹⁴ *See id.* at 1007:

Most antigens have a variety of antigenic determinants that stimulate the production of antibodies or T cell responses . . . even a single antigenic determinant will, in general, activate many clones [different antibody-producing cells], each of which produces an antigen-binding site with its own characteristic affinity for the determinant . . . Even . . . [a] . . . relatively simple structure . . . can be 'looked at' in many ways . . . [stimulating] . . . the production of hundreds of species of . . . antibodies, each of which is made by a different B cell clone.

An antibody binds to its antigen when the antigen fits into the complex three-dimensional space created by the variable regions of the antibody's heavy and light chains (see Figure 1, areas labeled VH & VL on the upper right "arm" of the "Y"). The diversity of antibodies produced by antigen stimulation is the result of the rearrangement of the genes that produce the variable regions of the heavy and light chains and result in the specific three-dimensional configuration of the "complementarity determining regions" (hereinafter "CDR") of the VH and VL (see the regions labeled "CDR" on the upper left hand "arm" of the "Y" in Figure 1).

The great leap forward in the ability to use antibodies as tools in biology and medicine came when Kohler and Milstein discovered that taking an individual B cell and fusing it with a tumor cell would result in an "immortal" hybrid cell, called a hybridoma, that would produce a cell line which could be maintained indefinitely in cell culture.¹⁵ Each daughter cell, or clone in the colony begun by a specific hybridoma, produces the same antibody as the original B cell fusion partner. Such immortalized B cell hybridoma cell colonies, or "clones," that produce antibodies of a single type are referred to as monoclonal, and the antibodies they produce are known as monoclonal antibodies.

The great advantage of Kohler and Milstein's breakthrough development of the technique for creating monoclonal antibodies is the ability to select a monoclonal antibody with desired characteristics and then to produce large quantities of the desired antibody by growing, dividing and growing still more colonies derived from the original hybridoma. Among the significant characteristics of an antibody are its specificity¹⁶ for a particular antigen and its affinity¹⁷ for that antigen. A desirable antibody for therapeutic purposes must be relatively specific for the target antigen and of a reasonably high affinity for the antigen. Of course the binding of the antibody to the particular antigen chosen must also have the desired therapeutic effect.

¹⁵ See *Johns Hopkins Univ. v. CellPro*, 152 F.3d 1342, 1351 n.14 (Fed. Cir. 1998).

¹⁶ Specificity is the propensity of an antibody to bind to a particular target antigenic determinant and in so doing to distinguish between the target and non-targets. See Alberts et al., *supra* note 13, at 178 ("[t]his [antigen-binding site of a monoclonal antibody] will recognize, for example, a particular conformation of a defined sequence of five or six amino acid side chains on a protein. Their uniform specificity alone makes monoclonal antibodies much more useful than conventional antisera").

While in Figure 1 the CDR regions appear to be flat, in fact they have a complicated three-dimensional structure that binds the target region, or epitope, of the antibody's target antigen. The amino acids that are linked together in the chain of the CDR region provide the three-dimensional structure of this antigen binding space and account for the specificity of the antibody's binding to its target. Two antibodies can bind the same antigen despite substantial differences in their CDR regions, so long as the antigen is large enough to provide multiple epitopes or antigenic determinants to which an antibody can bind. If the target of an antibody is a protein, it is certain to have multiple epitopes to which an antigen can bind. See Alberts et al., *supra* note 13, at 107.

¹⁷ Affinity is, more or less, the strength of the binding of the antibody to its target. The higher the affinity the more "tightly" an antibody binds to its antigen and the lower the percentage of antibodies that would be released from the antigen under particular conditions. See Alberts et al., *supra* note 13 at 1016--17.

In addition to specificity and affinity, antibodies also are characterized by their immunoglobulin class or subclass, such as IgG1, IgG2, IgA1, etc.¹⁸ Antibodies of different immunoglobulin types or subtypes may have naturally differing biological functions (such as the induction of cell-killing activity or the stimulation of the production of cytotoxic proteins).¹⁹ In addition, developers of antibody therapeutics may change or add to the antibody's mechanism of action by linking an active agent, such as a radioactive isotope, to the antibody.²⁰

Since Kohler and Milstein made possible the unlimited production of specific antibodies, researchers and biotechnology companies have seen the potential of monoclonal antibodies as “magic bullets”—biological molecules that can be specifically targeted to hone in on disease agents or diseased cells without unwanted effects on normal tissue or organs.²¹ Nonetheless, the first generation of monoclonal antibody therapeutics turned out to be largely a flop, due to an unanticipated problem with human patients' own immune systems responding to mouse-derived antibodies as foreign protein, a response known as HAMA, or Human Anti-Mouse Antibodies.²² The second generation of antibody therapeutics has attempted to overcome this in a number of ways, largely by “humanizing” the portions of the antibody that are not crucial to the antibody binding to its antigen.²³

¹⁸ See Richard A. Goldsby et al., Chapter 5: *Immunoglobulins: Structure and Function in Kuby Immunology 4e*, at <http://www.whfreeman.com/immunology/CH05/kuby05.htm> (last visited on April 23, 2003).

¹⁹ See *id.* “Antibody class or subclass is determined by the amino acid sequence of the constant region of the antibody, and determines the biological activity of that type of antibody.”

²⁰ E.g., IDEC Pharmaceuticals, <http://www.idecpharm.com/site/science/zevalin.htm> (last visited April 23, 2003): “Radioimmunotherapies like Zevalin™ are made by linking monoclonal antibodies – engineered in a laboratory to recognize and attach to substances on the surface of certain cells – to radioactive isotopes.” For a blocking antibody such as infliximab, the mechanism of action is quite simple, by binding to a portion of the target that ordinarily would bind to the target's natural biological target, the blocking antibody prevents that natural binding and the biological response that is ordinarily triggered. For such an antibody, all that matters is that the CDR region bind to some portion of the target in a way that obstructs normal binding. For a cytotoxic antibody, the mechanism of action is more complicated. Binding to an appropriate target is only the first step, the second step requires that the cell to which the target is attached be killed, which can occur through triggering an immune response to the target cell or by the antibody's attachment to a cell-killing substance, such as a radio-isotope or toxin.

²¹ See Jeffrey P. Kushdan, *Protein Patents and the Doctrine of Equivalents: Limits on the Expansion of Patent Rights*, 6 High Tech. L. J. 109, 115 n.20 (1991).

²² See S.K. Sharma et al., *Human Immune Response to Monoclonal Antibody-Enzyme Conjugates in ADEPT Pilot Clinical Trial*, Cell Biophys. Aug--Dec 1992, at 21(1-3):109--20; Edward G. Routledge et al., *Reshaping Antibodies for Therapy*, at <http://www.path.cam.ac.uk/~mrc7/reshaping/index.html> (last visited Apr. 23, 2003) [hereinafter Routledge et al.]. The reason that murine antibodies produce an immune “HAMA” response in humans is that a relatively small number of amino acids that differ between the murine and mouse antibody proteins cause the human immune system to respond to the murine antibody as non-self, or foreign. See M. Clark, *Antibody Humanization for Therapeutic Applications*, at <http://www.path.cam.ac.uk/~mrc7/humanisation/index.html> (last visited Apr. 23, 2003).

²³ Routledge et al., *supra* note 22.

A number of approaches have been developed to produce antibodies that do not produce a significant immune response directed at the antibody, resulting in successful antibody-based therapeutics, such as Centocor's Reopro® and Remicade®,²⁴ IDEC's Rituxan®²⁵ and Genentech's Herceptin®.²⁶ Each of these successful antibodies has had to resolve two problems. The first is HAMA, but the second, identifying a relevant antigen, is more challenging and far more diverse. While there are multiple solutions to the HAMA problem and each viable solution may work for a large number of different antibody therapeutics, the challenge of finding a clinically relevant antigen must be solved anew for every disease for which an antibody therapeutic is sought. At the same time, different approaches to solving HAMA may or may not make a difference in the efficacy of the antibody therapeutic. To date, the answer to whether the different major approaches to preventing HAMA make a difference in the efficacy of the antibodies has not been resolved.²⁷

The identification of clinically relevant targets for antibody therapeutics has progressed rapidly in recent years, both in cancer and in inflammatory disease. In cancer, the success of the lymphoma antibody Rituxan®, an unconjugated antibody to the CD20 marker on B-cells, was followed by the development of two subsequent radio-isotope-linked anti-CD20 antibodies, Zevalin® and Bexxar®.²⁸ Similarly, the success of an antibody to Tumor Necrosis Factor (TNF) in the treatment of Crohn's disease and juvenile rheumatoid arthritis (Remicade®) was followed by the approval of a second antibody to TNF (Humira®).²⁹ Tumor Necrosis Factor is also the target for another

²⁴ Reopro® is approved for the prevention of restenosis in conjunction with angioplasty, while Remicade® is approved for Crohn's disease and arthritis. *See* Reopro® (Abciximab), *at* http://www.centocor.com/cgi-bin/site/products/prod_reopro.cgi (last visited Apr. 23, 2003). Remicade® has orphan exclusivity for Crohn's disease and juvenile arthritis; *FDA List of Orphan Designations and Approvals*, *at* <http://www.fda.gov/orphan/designat/list.xls> (last visited July 23, 2003) [hereinafter "Orphan List"].

²⁵ Approved for non-Hodgkin's lymphoma. *See* IDEC Pharmaceuticals, *at* <http://www.idecpharm.com/site/science/rituxan.htm> (last visited Apr. 22, 2003). Rituximab® received orphan exclusivity for a subpopulation of non-Hodgkin's lymphoma patients. *See* Orphan List, *supra* note 24.

²⁶ Herceptin® is approved for metastatic breast cancer expressing the Her2 receptor. *See Genentech: In Business for Life*, *at* <http://www.gene.com/gene/products/information/oncology/herceptin/index.jsp> (last visited Apr. 23, 2003).

²⁷ *See* M. Clark, *The Therapeutic Antibody Human Homology Project* (TAHHP), *at* <http://www.path.cam.ac.uk/~mrc7/humanisation/TAHHP.html>, (last visited Apr. 23, 2003).

²⁸ *See* T.M. Illidge & M.C. Bayne, *Antibody Therapy of Lymphoma*, (Abstract) *at* http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11585011&dopt=Abstract (last visited Apr. 23, 2003) (discussing the development of Rituxan® (rituximab), Bexxar® (tositumomab) and Zevalin™ (ibrutumomab); *see also* *Brief*, *Washington Drug Letter*, Jan. 6, 2003, *at* Vol. 35, No. 1.

²⁹ *See* David Hamilton, "Abbott Enters Arthritis-Drug War with FDA Approval of Humira," *The Wall St. J.*, Jan. 2, 2003, *at* D4. Hamilton notes that Abbot's anti-TNF antibody will be competing against

arthritis disease, the non-antibody-based Enbrel®.³⁰ The evidence that the Epidermal Growth Factor Receptor (EGFR) is a potentially useful target for cancer drugs provides another example of competition to develop antibodies against a particular antigen. According to one report, five different EGFR-blocking antibodies have been developed so far.³¹ As these examples illustrate, antibody development is driven by the identification of potentially useful antigens and multiple antibodies can be developed to a clinically useful antigen.

Rituximab® and infliximab also represent two of the main types of antibody therapeutics: rituximab is an anti-cancer antibody that works by stimulating an immune response to the target cells, thus providing a reduction in tumor burden, while infliximab is an anti-inflammatory antibody that works by binding to a pro-inflammatory molecule (TNF-alpha) and blocking it from binding to its natural target. Blocking and cytotoxic antibodies represent the majority of antibody therapeutics to date, and each depends on the identification of a clinically effective target, or antigen. Cytotoxic antibodies require finding an antigen target for the diseased cells that will not cause unwanted targeting of normal cells while blocking antibodies require identifying an antigen target that plays a sufficiently important role in the disease process.

III. The FDA's Long Struggle To Interpret the Orphan Drug Act

When the Orphan Drug Act was signed into law in 1983, it put in place a variety of incentives for the development of new drugs for "orphan" disease populations of less than 200,000 patients in the United States.³² It also created a major regulatory problem for the FDA: how to administer its authority over the seven-year period of market exclusivity for pioneer sponsors of a new treatment for an orphan disease indication. Under the statute, there are two stages in the orphan drug development process: designation and approval. Designation simply requires an FDA determination that the disease indication proposed by the applicant is in fact an orphan disease within the terms

Centocor's Remicade® anti-TNF antibody and Immunex's Enbrel®, a soluble receptor that works to block TNF.

³⁰ *Id.*

³¹ See F. Ciardiello & G. Tortora, *A Novel Approach in the Treatment of Cancer: Targeting the Epidermal Growth Factor Receptor*, *Clinical Cancer Research* 29958-70, Oct. 7, 2001, available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11595683&dopt=Abstract (last visited Apr. 23, 2003) ("At least five blocking monoclonal antibodies have been developed against the EGFR.")

³² Or populations greater than 200,000 for which commercial development would not be undertaken because there is no reasonable expectation that the costs of development would be recovered. See *supra* note 5. The incentives, in addition to the seven year period of exclusivity for an approved orphan drug in its orphan market, 21 U.S.C. § 360cc (2000), include possible grants to defray the costs of clinical testing, 21 U.S.C. § 360ee(a) (2000), tax credits, 26 U.S.C. § 38(b) 12 (2000), and assistance with the design of clinical trials, 21 U.S.C. § 360aa (2000).

of the statute.³³ Designation can be sought at any time during the drug development process and is really without significance unless the drug development process is successful and leads to marketing approval. It is possible for more than one applicant to receive designation for the same or similar drugs and such competitions have recurred repeatedly.³⁴ The more significant problem for the FDA occurs after the first such sponsor receives approval to market an orphan drug. The Act provides:

[T]he Secretary may not approve another application under section 505 [21 U.S.C. § 355] or issue another license under section 351 of the Public Health Service Act [42 U.S.C. § 262] for such drug for such disease or condition for a person who is not the holder of such approved application, of such certification, or of such license until the expiration of seven years from the date of the approval of the approved application, the issuance of the certification, or the issuance of the license.³⁵

The problem has been and continues to be for the Secretary, or in reality, the FDA, to determine when another application is for “such drug for such disease.” The FDA’s initial response was to treat the new drugs produced by biotechnology, primarily proteins, which are very large biomolecules containing a hundred or more amino acids, in much the same way as more traditional drugs. Before the development of genetic engineering, drugs were commonly small molecules that were perhaps one-hundredth or even one three-hundredth the size of the average protein therapeutic. For such small molecule drugs, even small changes in the molecular structure were likely to result in appreciable differences in the drug’s biological effect. Thus the FDA took the view that for protein drugs, like small molecules, “such drug” was to be defined in terms of more or less absolute chemical identity. On this basis, the FDA proceeded to approve as orphan drugs two very similar versions of recombinant human growth hormone, the first by Genentech, the second by Eli Lilly.³⁶

The continued use of a strict definition of “same” for macromolecules would have had a disastrous effect on the exclusivity incentives of the Orphan Drug Act for biotechnology companies developing protein-based therapeutics. Unlike the traditional small molecules, it is generally quite easy to make small changes in a protein, such as substituting similar amino acids, without affecting its activity. The FDA responded by issuing new regulations, now codified in 21 C.F.R. § 316.3 (b)(13)(ii)(A)-(D) redefining “same drug” for large molecules.³⁷ In short, the FDA almost completely reversed the

³³ 21 U.S.C. §360bb (2003).

³⁴ See Bohrer & Prince, *supra* note 2. The fact that the prize of exclusivity goes to the winner of the race to marketing approval for a particular protein or antibody is a major reason why second entrants seek approval for a competitive entry into a small market and why the determination of sameness is so important.

³⁵ 21 U.S.C. §360cc.

³⁶ See *Genentech, Inc. v. Bowen*, 676 F. Supp. 301, 306 (D.D.C. 1987).

³⁷ Of particular relevance is the definition of “same drug” for proteins:

presumption made for traditional drugs: for small molecule drugs, only drugs with chemically identical active moieties (the principal active ingredient, regardless of its salt or ester formulation) are presumed to be the same; however, two proteins would be presumed to be the same even with minor differences in amino acid sequence, glycosylation,³⁸ or any other changes that occur after the gene encoding the protein has been translated into the primary amino acid sequence.

The FDA's revised regulations were a significant attempt to solve the problem of providing real protection for pioneer developers of protein therapeutics: no longer would the pioneer developer of a therapeutic protein for an orphan indication (such as for the long-term treatment of children who have growth failure due to a lack of adequate endogenous growth hormone secretion)³⁹ fear that a competitor could get approval simply by substituting one isoleucine for a leucine (or other very similar amino acid substitutes) in some region of the protein far from its active site. Instead, any competitor of a substantially similar protein would have to prove that their product provided a real additional benefit to patients, or, as the FDA termed it, "clinical superiority." Thus, whatever the degree of chemical difference between two similar protein-based drugs, if the second drug actually worked better, or caused fewer side effects, the demonstration of clinical superiority would conclusively establish that the second orphan drug applicant was different from the first one approved.

The FDA's effort to create a real barrier to "me-too" orphan drugs was a laudable one, but unfortunately, was soon shown to be porous. In *Berlex Laboratories, Inc. v. FDA*,⁴⁰ Berlex had received approval for interferon- β 1b for the treatment of multiple sclerosis. The "1b" designation refers to interferon- β produced in genetically engineered

(ii) If it is a drug composed of large molecules (macromolecules), a drug that contains the same principal molecular structural features (but not necessarily all of the same structural features) and is intended for the same use as a previously approved drug, except that, if the subsequent drug can be shown to be clinically superior, it will not be considered to be the same drug. This criterion will be applied as follows to different kinds of macromolecules:

(A) Two protein drugs would be considered the same if the only differences in structure between them were due to post-translational events or infidelity of translation or transcription or were minor differences in amino acid sequence; other potentially important differences, such as different glycosylation patterns or different tertiary structures, would not cause the drugs to be considered different unless the differences were shown to be clinically superior.

21 C.F.R. § 316.3(b)(13)(ii)(A) (2003).

³⁸ The attachment of carbohydrates to a protein is known as glycosylation and the resulting protein is a glycoprotein.

³⁹ See *Genentech*, 676 F. Supp. at 306. Genentech's orphan drug approval for recombinant human growth hormone was followed eight months later by the FDA's approval of Eli Lilly's version of recombinant human growth hormone, which differed from Genentech's by a single amino acid. Genentech's attempt to have the FDA's action overturned by the courts was unsuccessful, but the FDA did later revise their regulations, see 21 C.F.R. § 316.3, in an attempt to avoid a repetition of the Genentech-Lilly debacle.

⁴⁰ 942 F. Supp. 19 (D.D.C. 1996).

bacteria. Avonex then applied to the FDA for approval of its interferon- β 1a (produced in genetically engineered mammalian cells) for the treatment of multiple sclerosis. Berlex had tested its drug at a high dose delivered by subcutaneous injection every other day. Avonex had tested its drug at a much lower dose delivered once a week by intramuscular injection. Despite the lower dose, the drug still worked. Perhaps because of the lower, less frequent dose and different route of administration, the drug produced less injection site reactions and problems. Because of this better safety, or side effect profile, the FDA ruled that Avonex product was clinically superior and approved it. Avonex did not need to show that Berlex's pioneering orphan drug would not work similarly at the lower dose and route of administration. The District Court affirmed the FDA's discretion in its interpreting the "same drug" provision of the Orphan Drug Act.⁴¹

On the heels of its victory in *Berlex Labs*, the FDA realized that the approach it had taken to the "same drug" problem for proteins generally would almost certainly lead to repeated controversies in the rapidly emerging field of antibody therapeutics. The FDA's solution to the problem of determining "same drug" for antibody therapeutics was published as a Guidance for Industry in July of 1999.⁴² The Guidance is remarkable in its simplicity. The Guidance begins with a brief review of its interpretation of the Act for proteins the science of monoclonal antibodies and concludes that:

The proposed interpretation of sameness for two monoclonal antibodies is that two monoclonal antibody drugs would be considered the same if the amino acid sequences of the complementarity determining regions were the same or if there were only minor amino acid differences between them. Other potentially important amino acid differences outside the complementarity determining regions, or differences due to glycosylation patterns or post translational modifications would not per se cause the products to be considered different unless the subsequent drug was shown to be clinically superior.⁴³

In other words, two antibody-based drugs would be considered different if there were substantial amino acid differences in their CDRs and the same if there were not such substantial differences. This is despite the Guidance's acknowledgment that "[b]ecause of the many processes involved in generating antibody diversity, it is unlikely that independently derived monoclonal antibodies with the same antigen specificity will have identical amino acid sequences."⁴⁴ The FDA based its decision to determine "same drug"

⁴¹ See *id.*; see also Bohrer & Prince, *supra* note 2, at 395--96.

⁴² See Guidance, *supra* note 10, §§ IV and V.

⁴³ *Id.* § IV(B).

⁴⁴ See *id.*; see also Anthony S. Lubiniecki, Sc.D., Vice President of Smith Kline Beecham, *Letter to the FDA* (Oct. 22, 1999), available at <http://www.fda.gov/ohrms/dockets/dailys/102999/c0004.pdf> (last visited Oct. 18, 2002). Dr. Lubiniecki expresses a number of concerns about the FDA's position, including the concern central to this Article that:

for antibodies on the amino acid sequence of the CDR region in order to harmonize its application in this context with its general approach to macromolecules:

The definition of sameness for a macromolecule is based on its principal molecular structure. For the purpose of determining sameness of naked monoclonal antibodies under the Orphan Drug Act and its implementing regulations, the complementarity determining regions of the heavy and light chain variable regions will be viewed by the FDA as the principal molecular structural feature of a monoclonal antibody product.⁴⁵

While the FDA decision has the virtue of consistency, it ignores the difference between monoclonal antibodies and other macromolecules, particular proteins. While proteins are indeed generally defined by their principal molecular structure, antibodies are generally defined by their antigen. It is this decision of the FDA, to focus on the amino acid sequence of the CDR (antigen binding) regions of the monoclonal antibody therapeutic, that is likely to substantially undermine the incentives of the Orphan Drug Act. It provides the pioneer inventor with a very narrow scope of exclusivity and provides follow-on developers relatively easy entry into the market with a “me-too” orphan antibody therapeutic. It is very likely, as the FDA itself acknowledges, that two antibodies of similar specificity and affinity for the same antigenic determinant will have different amino acid sequences, even in their CDR.⁴⁶

IV. Matching Reward to Risk: An Antigenic Determination of Same Drug for Monoclonal Antibody Orphan Drugs

This section will address the problem of monoclonal antibody orphan drug “same” drug determinations in the general context of antibody drug discovery and development. By looking at orphan drug discovery in this context, one can better understand how the standard used to determine the scope of orphan drug exclusivity will impact the actual process of discovering and developing new antibody-based drugs for orphan disease indications. In particular, the thesis presented here is that the scope of orphan drug exclusivity should be related to the risk of orphan drug discovery and

Two monoclonal antibodies with very, different amino acid sequences within the CDRS could nonetheless bind to the same epitope with the same affinity, serve the same function, and provide the same therapeutic effect (see Kashmiri et al, 1999, copy attached). If “sameness” was defined solely on the basis of the amino acid sequence within the CDRS, FDA would apparently be forced to approve both monoclonal antibodies. Thus, FDA’s proposed approach could seriously undermine the primary incentive for orphan drug development intended by and provided by Congress in the Orphan Drug Act - exclusive marketing rights.

It is the purpose of this Article to propose a solution to the problem created by the FDA’s Guidance and recognized by Dr. Lubiniecki.

⁴⁵ See Guidance, *supra* note 10, § IV(B).

⁴⁶ *Id.*

development. The protection should be tailored to prevent second orphan drug applicants from a low-risk development effort that largely capitalizes on the discovery and development of the first approved orphan sponsor. In this way, the reward of orphan drug exclusivity is commensurate with the risk undertaken by the orphan drug developer. Any standard of exclusivity that allows second entrants to free-ride upon the discovery and development of first entrants would substantially undermine the value of orphan drug exclusivity and reduce the investment in developing treatments for orphan disease indications.⁴⁷

Drug discovery generally begins in one of two ways: either it begins with the serendipitous finding that a particular substance has an apparently medically useful property, as was the case with Alexander Fleming's discovery of the mold that produced penicillin,⁴⁸ or it begins with the discovery of a pathway or biological process that provides a target for drug discovery and development, as is increasingly the case in the era of genomics and proteomics.⁴⁹ Of course, even when a drug is found serendipitously, it immediately triggers a search for an understanding of its mechanism and its structure-function relationship, so that improved versions, second generation drugs, or competitive drugs can be developed.

Once a candidate drug that operates on a new pathway or target has been identified, it undergoes a variety of pre-clinical tests to determine its toxicology profile and its efficacy in animal models, followed by several increasingly large-scale tests for safety and efficacy in the appropriate human patient population.⁵⁰ If it is shown to be safe and effective for a major disease indication, it is likely to stimulate other companies to develop drugs aimed at the same pathway, perhaps even before the first drug is approved by the FDA. These second entrants rush to identify new chemical entities that act on the same target because the work of the earlier "pioneer" company, demonstrating the clinical utility of the target, substantially reduces the risk of their own development

⁴⁷ See Bohrer & Prince, *supra* note 2, at 365. In this earlier article, the difference between the scope of exclusivity for traditional small-molecule drugs and protein drugs was analyzed, however the problem of antibody therapeutics was not addressed.

⁴⁸ See *A Science Odyssey: People and Discoveries*, at <http://www.pbs.org/wgbh/aso/databank/entries/dm28pe.html> (last visited Apr. 23, 2003). Fleming noticed that staph bacteria were not growing in the vicinity of a mold that had contaminated one of the cultures in his laboratory. His observation led him to the breakthrough discovery of the first powerful antibiotic.

⁴⁹ See *Creating Medicines*, at <http://science.gsk.com/m2m/randd.pdf> (last visited Apr. 23, 2003) (GlaxoSmith Kline document providing an overview of drug development). An example of target-based drug discovery can be seen in the field of anti-hypertensives, for example in the number of ACE inhibitors that all are aimed at blocking the workings of a particular target "angiotensin converting enzyme" or ACE. See D. MacAreavey & J. Robertson, *Angiotensin Converting Enzyme Inhibitors and Moderate Hypertension* 40 *Drugs* 326 (1990) (discussing the numerous different drugs aimed at that target as well as the advantages and disadvantages of particular ACE inhibitors).

⁵⁰ See James Thuo Gathii, *Rights, Patents, Markets and the Global Aids Pandemic*, 14 *Fla. J. Int'l L.* 261, 334-40 (2002) (discussing the FDA testing and review process in the context of barriers to competition in the global pharmaceutical marketplace).

efforts.⁵¹ In the biggest therapeutic categories, such as anti-cholesterol agents, anti-depressants, and anti-hypertensives, there are numerous agents competing in a category and several in each disease category are aimed at the same target: statins for cholesterol;⁵² selective serotonin-reuptake inhibitors for depression;⁵³ and multiple beta blockers or ACE inhibitors for hypertension.⁵⁴ These therapeutic categories are large enough to induce the development of multiple drugs, with sometimes small chemical and pharmacological differences, each generating a profit. For these large patient population indications, pioneer drug developers are not deterred by the knowledge that any new target developed with clinical utility will quickly be pursued by other drug companies. The pioneer developer's additional risk in developing a drug for a previously unproven target is generally rewarded by the brand recognition and market share that accrue to the first entrant into a new therapeutic category with a very large potential patient population.⁵⁵

Of course, the rationale for the Orphan Drug Act's exclusivity provisions was to provide an inducement for the development of drugs for smaller markets, where multiple entrants would make the market unprofitable for all. Because of this, it is particularly

⁵¹ See U.S. Congress, Office of Technology Assessment, *Pharmaceutical R&D: Costs, Risks and Rewards*, OTA-H-522 (1993), available at http://www.wws.princeton.edu/~ota/ns20/alpha_f.html (last visited Apr. 3, 2003). In that study the OTA found that:

The discovery and development of NCEs [new chemical entities] is the heart of pharmaceutical R&D, because the developers of follow-on or generic products build on the knowledge produced in the course of developing them. The market for the compound and all its follow-on products or generic copies in future years rests on the R&D that led to its initial introduction to the market

. . . .

NCE's comprise two poorly-defined subcategories: pioneer drugs and "me-too" drugs. Pioneer NCEs have molecular structures or mechanisms of action that are very different from all previously existing drugs in a therapeutic area. The first compound to inhibit the action of a specific enzyme, for example, is a pioneer drug. Me-too drugs are introduced after the pioneer and are similar but not identical to the pioneer compounds in molecular structure and mechanism of action. Many me-too drugs are developed through deliberate imitation of the pioneer compound and have a shorter and more certain discovery period. But, the R&D cost advantage gained by imitation is typically met by a reduction in potential dollar returns by being a late entrant to the market.

Id. at 6--7 [citations omitted].

⁵² *American Hospital Formulary Service Drug Monographs* 24:06.08 (1997) (discussing Simvastatin®, Pravastatin®, Lovastatin® and Atorvastatin®).

⁵³ *American Hospital Formulary Service Drug Monographs* 28:16.04 (1997).

⁵⁴ *American Hospital Formulary Service Drug Monographs* 24:24, 24:32.04 (1997).

⁵⁵ See U.S. Congress, Office of Technology Assessment, *supra* note 51.

important to provide pioneers with protection against “me-too” entrants into the market.⁵⁶ In the context of the Orphan Drug Act, this protection against “me-too” entrants takes the form of a seven-year period of exclusivity where the FDA will not approve the “same” drug for the same indication. As discussed above,⁵⁷ the FDA has recognized for some time that protein-based therapeutics present a different challenge for Orphan Drug Act exclusivity determinations than small-molecule chemically synthesized pharmaceuticals. The FDA’s approach to the problem has been to continue to focus on chemical identity as the first principle by which exclusivity determinations should be made, while attempting to accommodate the challenges of protein therapeutics by loosening the standard from chemical identity to “minor amino acid differences” in the CDR.⁵⁸ The FDA’s use of “minor amino acid differences” is an attempt to define a structure-based standard that bars minor changes in proteins that do not alter the three-dimensional structure of the protein to an extent that would affect the protein’s biological activity. Such a chemical-identity approach is workable for protein drugs that are copies of naturally-occurring, secreted proteins that operate by binding to receptors. It would indeed be difficult for a would-be orphan drug copyist to make substantial changes to the amino acid sequence of erythropoietin, human growth hormone, or interferon- β ⁵⁹ without losing the desired biological activity. In the antibody field, the FDA Guidance uses this same concept of amino acid sequence similarity and specifically applies it to the portion of the antibody that binds to its target antigen, which is known as its CDR.⁶⁰

However, antibody drugs are different. While a would-be copyist who tried to make changes to a successful pioneer antibody would indeed find it difficult to significantly alter the antibody, in the case of monoclonal antibodies to the same antigen produced by different laboratories, it is quite possible for there to be significant differences in the amino acid sequence of two, independently-developed antibodies, even in the CDR regions that are the focus of the FDA’s proposed guidance for “same drug” determinations for orphan drug monoclonal antibodies.⁶¹ As discussed in Part II of this

⁵⁶ See *id.* As the OTA study notes, the distinction between pioneer and “me-too” can be “fuzzy” when the development of the first entry based on a new target or pathway is competitive, with multiple companies in a race to be the first to win approval. In these cases, the losers may have costs just as high as that of the successful pioneer.

⁵⁷ See *supra* text accompanying notes 6--8.

⁵⁸ See Guidance, *supra* note 10, § IV(B).

⁵⁹ See Bohrer & Prince, *supra* note 2, at 395--401, which deals at length with the interferon- β orphan drug controversy. In that case, there was almost no amino acid variation between the two competitor orphan drug entrants, but differences in administration lead to adverse effect differences that produced a finding of “clinical superiority.”

⁶⁰ See Guidance, *supra* note 10, § IV(A)--(B).

⁶¹ To summarize the distinction between other kinds of protein therapeutics and antibodies, the relationship between a traditional protein and its receptor requires conservation of amino acid sequence, while the relationship between antigen and antibody permits antibody diversity. See Alberts et al., *supra* note 13. The FDA Guidance itself acknowledges that “[b]ecause of the many processes involved in generating antibody diversity, it is unlikely that independently derived monoclonal antibodies with the same antigen

Article, it is not only scientifically likely that different antibodies to the same antigen will both be clinically effective, but it has already been the case that multiple antibodies will be developed against a particular clinically relevant antigen.⁶² The problem for orphan drug exclusivity is adequately protecting the first developer of an antibody that successfully targets a particular antigen for the treatment of an orphan disease. To achieve this, the FDA should define antibody “sameness” by the antigen to which the antibody joins, not by amino acid sequence.⁶³ While developers of additional antibodies to an antigen that has been shown to be clinically significant certainly face some risk, they will generally face much less risk than did the pioneer entrant who demonstrated the utility of the target.

What then would be the definition of “same drug” for antibody therapeutics? Two antibodies with the same mechanism of action⁶⁴ would be considered the same drug for Orphan Drug Act exclusivity if they both targeted the same antigen for the treatment of the same orphan indication, unless the second antibody therapeutic was demonstrated to be clinically superior to the prior-approved antibody therapeutic. How would an antigen-focused presumption of sameness compare with the FDA’s CDR-focused sameness standard in satisfying the three criteria for a reasonable solution to the orphan drug sameness problem for antibodies?⁶⁵ With respect to the first criteria, insuring that there is a sufficient incentive for undertaking the risky process of drug development, the antigen presumption clearly broadens the scope of protection to pioneer orphan antibody developers, thus providing a greater incentive than the FDA’s standard. Second, the antigen presumption provides pioneer developers with a relatively clear understanding of the scope of their protection. Third, the antigen presumption similarly provides would-be second orphan antibody developers a clear understanding of their chances of approval

specificity will have identical amino acid sequences.” Guidance, *supra* note 13, § II. However, the FDA did not recognize the significance of this basic scientific fact for orphan drug exclusivity.

⁶² See sources cited *supra* notes 28--29 (discussing multiple antibodies to CD20 (lymphoma) and TNF (inflammatory disease)).

⁶³ See *Comment of Antisoma on the FDA’s Proposed Guidelines*, at <http://www.fda.gov/ohrms/dockets/dailys/092399/c00001.pdf> (last visited on February 21, 2003):

Based on the above discussion points our comment on the draft guidelines would be to allow the remit of Orphan Status Protection to include an element of functionality. That is when an antibody is against the same target antigen and has the same effector it should be regarded as being the same for orphan drug purposes irrespective of the binding site sequence of the antibody.

In the course of my research for this Article, I found that Antisoma’s brief comment on the guidelines supports the notion that biotechnology companies would support the policy argument made here. *But see Comment of Centocor*, at <http://www.fda.gov/ohrms/dockets/dailys/100899/c000002.pdf> (last visited Feb. 21, 2003) (“We have carefully reviewed the draft and have no suggestions for changes. The definition of “sameness” based on the complementarity determining regions as the principal structural feature of the antibody molecule provides reasonable protection of orphan drugs and has a sound scientific basis.”).

⁶⁴ See *supra* text accompanying notes 16--19.

⁶⁵ See *supra* text accompanying note 8.

and a roadmap to second antibody approval. If the second antibody is aimed at the same antigen, it must either have a different mechanism of action (e.g. radioactive versus non-radioactive) or demonstrate in clinical trials that it is superior to the pioneer antibody either in efficacy or safety.

The FDA's administration of the Orphan Drug Act has always recognized that while the exclusivity protection against competition from the same drug was central to the Act, the exclusivity provisions should not be used as a barrier to the development of superior therapeutics. The FDA Orphan Drug Regulations were intended "to ensure that improved therapies will always be marketable, and that orphan drug exclusive approval does not preclude significant improvements in treating rare diseases."⁶⁶ The FDA introduced the concept of "clinical superiority" to accommodate the need to allow significant improvements in the treatment of orphan indications which might otherwise be barred from approval by similarity to a previously approved orphan drug. In the context of antibody therapeutics for orphan drugs, under this approach clinical superiority would be the means by which developers of second antibody therapeutics to the same antigen could prove their antibody sufficiently different to warrant approval. A second antibody developer that has chosen a different method of reducing the immunogenicity of an originally murine antibody may well be able to establish that its antibody produces a longer lasting biological effect, or otherwise improves patient care.⁶⁷ Conversely, the first company to demonstrate that an antibody directed against a particular antigen is safe and effective for the treatment of an orphan indication would be entitled to market exclusivity against antibodies targeting the same antigen until one of those antibodies was shown to be safer or more effective. Thus both first and second orphan antibody developers would have a much clearer understanding of when the demonstration of clinical superiority would be required.

At this point, we can look at a hypothetical conflict between two currently marketed antibodies, infliximab, marketed as Remicade® by Centocor,⁶⁸ and Adalimumab, marketed as Humira™ by Abbott Laboratories.⁶⁹ Both are antibodies to the same antigen, tumor necrosis factor alpha, a cytokine (or chemical messenger) that plays a key role in producing inflammation.⁷⁰ Remicade® was approved first and received orphan drug exclusivity for moderately to severely active Crohn's disease resistant to

⁶⁶ 56 Fed. Reg. 3338, §1 para. 3.

⁶⁷ See M. Clark, *Antibody Humanization for Therapeutic Applications*, at <http://www.path.cam.ac.uk/~mrc7/humanisation/index.html> (last visited on Apr. 23, 2003) for a general discussion of antibody humanization techniques and issues.

⁶⁸ See Description of Remicade® Drug at http://www.centocor.com/cgi-bin/site/products/prod_remicade.cgi (last visited July 20, 2003).

⁶⁹ See Description of Humira™ Drug at <http://www.rxabbott.com/pdf/humira.pdf> (last visited July 20, 2003).

⁷⁰ See *id.*

conventional therapy⁷¹ as well as non-orphan marketing approval for various indications in rheumatoid arthritis.⁷² Humira™ also received approval for use in various arthritis indications. There is no actual orphan exclusivity battle between Humira™ and Remicade®, since Abbott has not sought to have the FDA approve its antibody for use against Crohn's disease, Centocor's orphan indication. However, we can hypothesize such an attempt and compare the results of applying FDA's current policy and our proposed policy. Under the FDA's current policy, to determine approval of Abbott's orphan Crohn's indication application, the FDA would evaluate whether the two antibodies had the same or very similar amino acid sequences in their CDR or antibody-binding regions. The fact that Humira™ is a recombinant human antibody while Remicade® is a chimeric antibody (having a murine antibody-binding domain engrafted into a human IgG constant region)⁷³ certainly raises doubts as to whether the two antibodies share substantial homology in the antibody-binding regions. There would not have been much certainty, either from Centocor's perspective or Abbott's, about the scope of Humira's™ protection prior to the introduction of both drugs, though either one could use available laboratory techniques to determine the relevant amino acid sequences to predict the FDA's response *ex post*. Conversely, it is clear that under the test proposed here, Abbott would know that the only way to have their antibody approved in light of Centocor's prior approval would be to demonstrate that Humira™ was clinically superior, that is, offers a significant benefit to patients over Remicade®.

V. Conclusion

The Orphan Drug Act provision for seven years of exclusivity against competition by the same drug for the same indication was intended to provide a significant incentive for undertaking the costly and risky process of drug development where the size of the patient population would limit ordinary commercial incentives. For larger patient populations, drug developers know that they will likely face competition by similar drugs and knowingly bear the risks of drug development to capture the rewards that accrue to the first to establish a new therapeutic category. The Orphan Drug Act, however, was predicated on the assumption that smaller patient populations needed an assured market size, free from "me-too" competition, to induce development and provide adequate returns to the pioneer developer.

The FDA's experience with the first major biotechnology-produced products, proteins, convinced the FDA that protein therapeutics required a relaxed standard that would presume two proteins to be the same if there were no more than "minor differences in amino acid sequence." The focus on amino acid sequence for non-antibody proteins

⁷¹ See List of All Orphan Products Approved at <http://www.fda.gov/orphan/designat/allap.rtf> (last visited July 17, 2003).

⁷² See *supra* note 68.

⁷³ *American Hospital Formulary Service Drug Monographs* 92:00 (Remicade® is listed under Infliximab, Humira™ is listed under Adalimumab).

works because the general amino acid sequence determines the biological function of the protein. For antibodies, however, the amino acid sequence in the antigen-binding region, or CDR, that is the focus of the FDA's proposed Guidance for Industry, does not determine the antibody's function in the same way that amino acid sequence determines an enzyme's function. Rather, it is the antigen that will primarily determine the efficacy of a particular antibody, and it is the proof that an antigen is clinically useful in the treatment of a disease that provides the biggest risk in antibody development. The approach to orphan drug exclusivity recommended here is that the FDA presumes antibodies of the same immunoglobulin class and with the same mechanism of action⁷⁴ to be the same drug unless the second antibody is shown to be clinically superior to the first. This focus on the antigen would provide a substantial amount of certainty to the developers of antibody therapeutics for orphan indications, provide real protection against "me-too" antibodies, yet leave sufficient room for innovative antibody development to provide evidence of significant therapeutic advantage.

⁷⁴ See *supra* text accompanying note 16. Two IgG antibodies targeting the same antigen without attached isotopes or toxins would be the same, while two radioactively tagged IgG antibodies would be considered the same, regardless of whether different isotopes were used, unless the second was shown to offer a significant therapeutic advantage warranting a finding of clinical superiority.