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Client Alert

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The Noose Tightens on Patent Protection of Biologics?

Biologics continue to increase in number, both in approved products and in products in development. Many of the biggest selling products are biologics, and in particular biologics arising from a monoclonal antibody. 21 FDA approved therapies – including eight blockbuster drugs, are monoclonal antibody based. In 2007, the US market was worth $21.9bn. (Bioportfolio, Therapeutic Monoclonal Antibody Report 2008-2023). For example, some of the biggest are Remicade® (Johnson & Johnson, Schering-Plough, Tanabe) and Enbrel® (Amgen, Wyeth) for Rheumatoid arthritis, Rituxan®, (MabThera Roche, Genentech, Biogen Idec, Chugai Pharmaceutical) for Non-Hodgkin's lymphoma and Herceptin® (Roche, Genentech, Chugai Pharmaceutical) for Breast cancer rank 12, and Avastin® (Roche, Genentech) for Colorectal cancer, having combined worldwide sales of over $20bn in 2008. (Krishan Maggon, https://knol.google.com/k/krishan-maggon/world-top-ten-biotechnology-biologics/3fy5eowy8suq3/16#).

This exists for many reasons, not the least of which are certain advantages in competition from generics and in the ability (in the past) to get broader patent protection covering the active molecule, such as the antibody. While congress considers the follow-on biologic legislation which would pave the way for biologic generics (S 1695, The Biologics Price Competition and Innovation Act of 2007), the Federal Circuit just recently reduced patent protection of monoclonal antibody biologics in its recent opinion in In re Alonso 2008-1079.

Under 35 USC § 112, an inventor must provide a "written description" of the invention before a patent will be granted. This written description requirement blocks many biotechnology and pharmaceutical patent applications from maturing into patents. An inventor meets this written description requirement of a genus of molecules by "disclosing: (1) a representative number of species in that genus; or (2) its "relevant identifying characteristics," such as "complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." In re Alonso, page 6, *citing* Enzo, 323 F.3d at 964. This can be particularly problematic for biotechnology related inventions as much of biotechnology arises from functional relationships without knowing precise structure, rather than a more traditional chemical world, where structure of a molecule is king. Antibodies used in biologics represent just such a situation. Biotechnologists

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know how to use a monoclonal antibody for example, without knowing the structure of the monoclonal antibody, and biotechnologists know how to obtain any monoclonal antibody for an antigen without knowing the structure of the antibody, or even the antigen. In fact, the ability to identify the antibody having the desired characteristics, and have the antibody function as desired, without knowing the structure or the precise way in which it interacts with the antigen, is the very characteristic that can make them an attractive alternative to traditional pharmaceutical identification and development which requires much more "knowledge" to identify useful compounds.

The United States Government denied Kenneth Alonso a patent covering

> [a] method of treating neurofibrosarcoma in a human by administering an effective amount of a monoclonal antibody idiotypic to the neurofibrosarcoma of said human, wherein said monoclonal antibody is secreted from a human-human hybridoma derived from the neurofibrosarcoma cells.

In re Alonso at page 2.

This claim covers a method of treating neurofibrosarcomas using monoclonal antibodies which are idiotypic to the neurofibrosarcoma, i.e. antibodies binding the epitope defining the neurofibrosarcoma. Mr. Alonso presented data in his application using his method of identifying the antibodies, to treat a human patient *successfully*. Yet, the Federal Circuit determined that the claim 92, set forth above, was invalid for violating the written description requirement because the "single monoclonal antibody" identified by Mr. Alonso was not representative of the genus of monoclonal antibodies covered by the claim as the very nature of claim addressed the issue that the idiotype of a neurofibrosarcoma in different patients may be different.

Patents covering monoclonal antibodies had long had a bit of a protective hedge. Generally, if an antigen was known, a general class of antibodies binding the antigen were considered obvious under 35 USC § 103, but a specific monoclonal antibody was not, and likewise if an antigen was novel, the general class of antibodies was considered non-obvious and enabled. There was not direct law on the issue of whether an antibody or class of antibodies, had written description if the antigen was known. In fact, this was supported by the Federal Circuit opinion in Noelle v. Lederman (Fed. Cir. 2004), which found that written description was lacking when the antigen was not fully characterized. What is different in In re Alonso then?

The holding in *In re Alonso* turns on the scientific fact that the class of antibodies has an "unpredictable" antigen. The court found that because the antigen was defined as "idiotypic of neurofibrosarcoma" that this antigen would have a different unpredictable structure for each patient for whom an antibody was generated. Thus, under Noelle, the antigen was not specifically defined enough to allow for the Alonso claim to stand.

While it is true, that within the Alonso claim the antigen may be different, under the reading given by the court, is really true that the skilled artisan would not have understood that Mr. Alonso was in possession

of the claimed invention? Those seeking patents for monoclonal antibodies will seek to limit Alonso to its specific facts, but there is broad language in the opinion by the court which leaves open the possibility that because not enough structural information was known about the antibodies themselves, that future opinions may seek to limit claims along these lines.

In conclusion, what is clear after Alonso, is that applicants seeking patent protection for monoclonal antibodies should maximize the information about the structure of the antibody class in the patent application, as well as characteristics about the binding of the antibody, such as affinity or specificity. Applicants should also maximize information about the epitope so as to define the epitope to avoid the situation in Alonso where the epitope was changing without a predictability of the structural class that would define those epitopes. The full effect of Alonso remains be seen, but there has been at least a slight reduction in the strength of patents covering monoclonal antibodies.