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IN THE UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

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| GENENTECH, INC., Plaintiff, vs. CENTOCOR, INC., Defendant. | Case Number C 94-01379 BAC<br><br>AFFIDAVIT OF JOHN GHRAYEB, Ph.D.<br><br>Date: August 26, 1994<br>Time: 9:00 a.m.<br>Dept: Courtroom 5, 17th Floor |

COMMONWEALTH OF PENNSYLVANIA :
: ss
COUNTY OF CHESTER :

DR. JOHN GHRAYEB, being duly sworn, deposes and says:

1. I am the Vice President of Pharmaceutical Research of Centocor, Inc. I make this affidavit in support of Centocor's motion for summary judgment. While my job title has changed over the years, I have been personally

involved with Centocor's research and development efforts in the monoclonal antibody field since 1984.

2. The c7E3 product is a fragment of a chimeric antibody which is intended to inhibit the formation of blood clots in the cardiovascular system. A chimeric antibody is a protein molecule which derives certain portions of its structure from one mammalian species (here a mouse) and other portions from a second species (here a human).

3. Centocor first began work on the anti-clotting drug ultimately known as c7E3 in 1986. In March of that year, it received a live culture of the murine (or mouse) hybridoma cell, 7E3, from Dr. Barry S. Coller of the State University of New York at Stony Brook ("SUNY"). This hybridoma cell resulted from a fusion of a mouse antibody-producing cell and a mouse myeloma cell, a cell capable of immortalizing the resulting fusion, that is, making it capable of continued cell division under culture. The antibody secreted by 7E3 binds specifically to a glycoprotein found on human blood platelets and thereby inhibits a step involved in the formation of blood clots. Centocor licensed 7E3 from SUNY to pursue research in the area of anti-clotting agents of potential benefit to patients at risk of the injurious consequences of blood clots. More generally, Centocor's focus has been on various antibody-derived diagnostic and therapeutic products since its founding.

4. In 1987, Centocor isolated and cloned the DNA sequences from the so-called variable region genes in 7E3. These sequences are those which contain the genetic code for the portion of the 7E3 antibody responsible for its specific binding properties -- the variable regions of the so-called heavy and light chains making up the complete antibody.

5. A mouse or human antibody is composed of four chains, two heavy and two light, each with a variable region and a constant region. Different genes within an antibody-producing cell "express" different segments of the various chains, which are then assembled within the cell into complete antibodies.

6. The cloned variable region DNA sequences were then inserted into expression vectors constructed by Dr. Vernon T. Oi and Dr. Sherie L. Morrison and licensed by Centocor from Stanford and Columbia Universities. These vectors -- means of inserting DNA from one source into another cellular context -- contained human antibody constant regions and related expression sequences. Thus, when the variable region DNA sequences were added, the vectors ended up containing the DNA coding for complete heavy and light chains.

7. Centocor succeeded by the end of 1987 in "transfecting" (or inserting) each of these vectors into a single non-antibody secreting cell of murine myeloma origin. The cell thus transfected, called a "transfectoma", was

demonstrated to have the capability of secreting an intact and biologically active (or functional) four chain antibody. The antibody was chimeric; that is, the variable regions were derived from the mouse 7E3 and the constant regions were of human antibody derivation.

8. The transfectoma from which c7E3 is derived was created on September 19, 1988. This represented a continuation of the work begun at the end of 1987; and the same vectors were used. The September 19, 1988 transfectoma cell was subsequently subcloned to select a cell line capable of high level production of c7E3 to be used in clinical trials. The actual clinical product used by Centocor is an antibody fragment which retains the binding characteristics of the whole antibody. It is produced by cleaving the whole antibody with an enzyme which correctly selects the desired fragment. All of this research and development activity occurred prior to the issuance of the Genentech '567 patent.

9. Shortly after receiving the 7E3 cell line, Centocor commenced toxicologic, pharmokinetic and pharmacologic testing of the 7E3 antibody and fragments thereof, including testing in animal models. Upon creation of transfectoma cell lines, similar testing began with c7E3 and fragments thereof. Such testing is required by the FDA

prior to the commencement of any clinical trials with human subjects.

JOHN GHRAYEB, Ph.D.

Sworn to and subscribed
before me this 13th
day of June, 1994.

NOTARY PUBLIC

Notarial Seal
Beverly C. Halvorsen, Notary Public
Malvern Boro, Chester County
My Commission Expires July 21, 1997