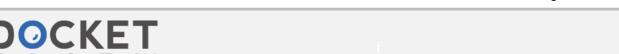
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9	Attorneys for Defendant,
10	CENTOCOR, INC.
11	IN THE UNITED STATES DISTRICT COURT
12	NORTHERN DISTRICT OF CALIFORNIA
13	GENENTECH, INC., ) Case Number C 94-01379 BAC
14	Plaintiff, )
ļ	) AFFIDAVIT OF ) JOHN GHRAYEB, Ph.D.
15	
16	/ CENTOCOR, INC., ) ) Date: August 26, 1994
17	Defendant. ) Time: 9:00 a.m. Dept: Courtroom 5, 17th Floor
18/	
19	COMMONWEALTH OF PENNSYLVANIA : ss
20	:
21	COUNTY OF CHESTER :
22	DR. JOHN GHRAYEB, being duly sworn, deposes and
<b>2</b> 3	says:
24	1. I am the Vice President of Pharmaceutical
25	Research of Centocor, Inc. I make this affidavit in support
26	of Centocor's motion for summary judgment. While my job
27 27	title has changed over the years, I have been personally
1	order into ondingen over the first first the first fir
28	AMBIDANTO OF JOHN CHRAYER, Ph.D.



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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).
- Centocor first began work on the anticlotting 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"). hybridoma cell resulted from a fusion of a mouse antibodyproducing 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. 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.

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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.
- 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

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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.

- 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

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prior to the commencement of any clinical trials with human subjects. Sworn to and subscribed before me this 13th day of June Notarial Seal Beverly C. Haivorsen. Notary Public Maivem Boro, Chester County My Commission Expires July 21, 1997 NOTARY PUBLIC 3 -5-AFFIDAVIT OF JOHN GHRAYEB, Ph.D.

