In the Matter of

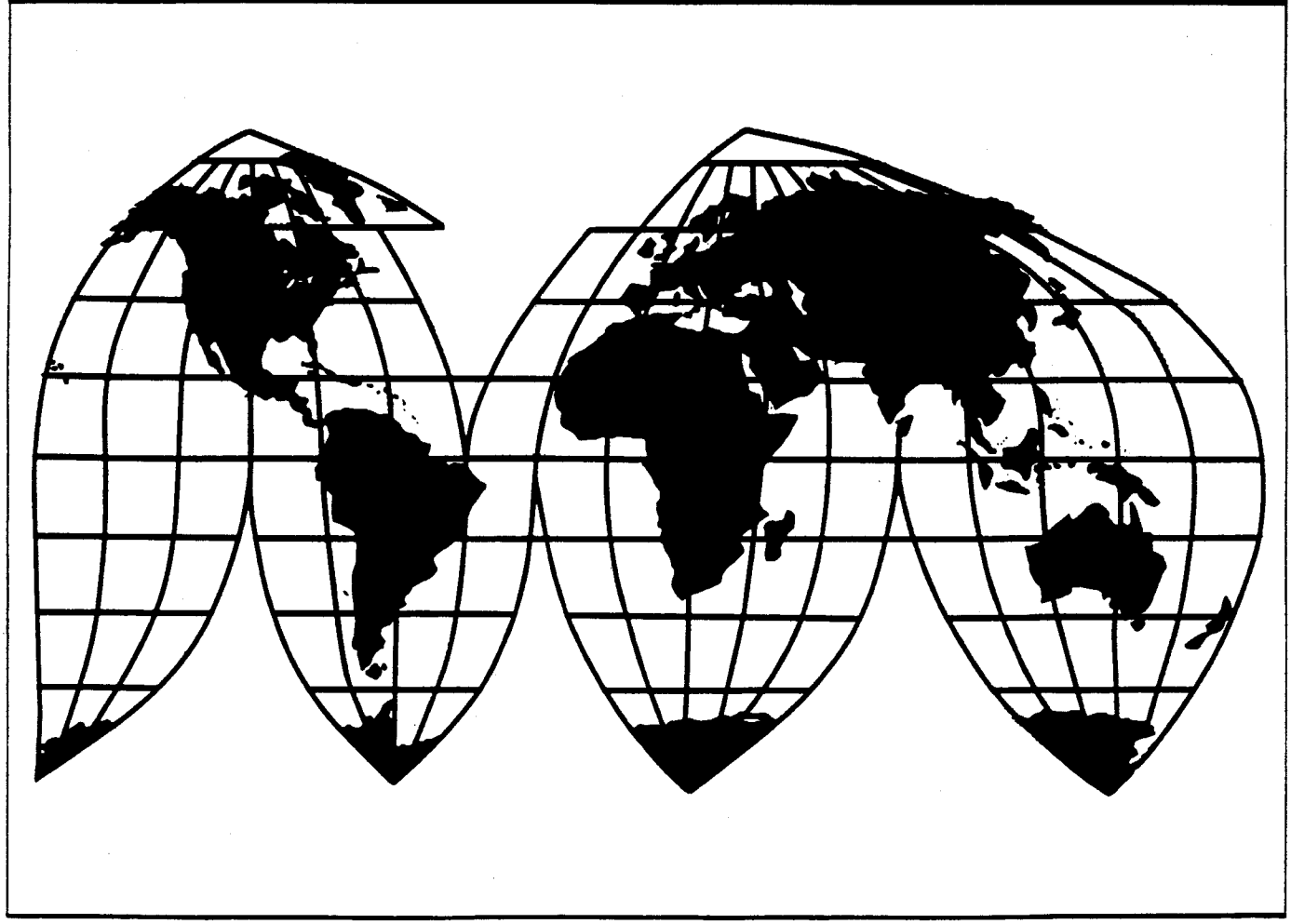
Certain Recombinantly Produced Human Growth Hormones

Investigation No. 337-TA-358

Temporary Relief Proceedings

Publication 2764 **March 1994**

U.S. International Trade Commission



Washington, DC 20436

U.S. International Trade Commission

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UNITED STATES INTERNATIONAL TRADE COMMISSION
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In the Matter of CERTAIN RECOMBINANTLY PRODUCED HUMAN GROWTH HORMONES	Investigation No. 337-TA-358

NOTICE OF COMMISSION DETERMINATION TO ADOPT THE ADMINISTRATIVE LAW JUDGE'S INITIAL DETERMINATION DENYING THE MOTION OF COMPLAINANT FOR TEMPORARY RELIEF

AGENCY: U.S. International Trade Commission.

ACTION: Notice.

SUMMARY: Notice is hereby given that the U.S. International Trade Commission (Commission) has determined to adopt the presiding administrative law judge's (ALJ) initial determination (ID) in the above-captioned investigation denying complainant Genentech, Inc.'s motion for temporary relief.

FOR FURTHER INFORMATION CONTACT: Jean Jackson, Esq., Office of the General Counsel, U.S. International Trade Commission, telephone 202-205-3104.

SUPPLEMENTARY INFORMATION: The Commission instituted this investigation on September 29, 1993, based on a complaint filed by Genentech, Inc. of South San Francisco, California. 58 Fed. Reg. 50954. The following firms were named as respondents: Novo Nordisk A/S of Denmark; Novo Nordisk of North America, Inc. of New York; ZymoGenetics, Inc. of Seattle, Washington (collectively, the Novo respondents); Bio-Technology General Corp. of New York; and Bio-Technology General Corp. (Israel) Ltd. (collectively, the BTG respondents). The Commission also provisionally accepted Genentech's motion for temporary relief. Id. The Commission terminated the temporary relief proceedings as to the Novo respondents on the basis of a consent order. 58 Fed. Reg. 60672 (November 17, 1993).

The presiding ALJ held an evidentiary hearing on temporary relief from December 13-18, 1993. On January 26, 1994, the ALJ issued an ID denying Genentech's motion for temporary relief. On February 7, 1994, the parties filed written comments concerning the ID. Parties filed reply comments on February 11, 1994. No government agency comments were received.

This action is taken under the authority of section 337 of the Tariff Act of 1930, 19 U.S.C. § 1337, and Commission interim rule 210.24(e).

Copies of the ID and all other nonconfidential documents filed in connection with this investigation are available for inspection during official business hours (8:45 a.m. to 5:15 p.m.) in

the Office of the Secretary, U.S. International Trade Commission, 500 E Street S.W., Washington, D.C. 20436, telephone 202-205-2000. Hearing-impaired persons are advised that information on the matter can be obtained by contacting the Commission's TDD terminal on 202-205-1810.

By order of the Commission.

Donna R. Koehnke
Secretary

Issued: February 25, 1994

PUBLIC VERSION

Business confidential information has been deleted.

UNITED STATES INTERNATIONAL TRADE COMMISSION
Washington, D.C. 20436

In the Matter of	)	
	)	
CERTAIN RECOMBINANTLY PRODUCED	)	
HUMAN GROWTH HORMONES	)	Investigation No. 337-TA-358
	)	
	)	

Order No. 64: Initial Determination Denying Complainant's Motion No. 358-1 For Temporary Relief

Section 210.53 of the Commission's interim rules requires that Order No. 64 be called an initial determination so that it can be reviewed by the Commission even if no petition for review is filed. This is not the final decision of the administrative law judge in this investigation, which also will be called an initial determination. Pursuant to Commission interim rule 210.24(e)(17), this initial determination shall become the determination of the Commission thirty (30) calendar days after issuance thereof, unless the Commission modifies or vacates the initial determination within that period.

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ABBREVIATIONS

CB	Complainant's Brief
CBR	Complainant's Reply Brief
CPX	Complainant's Physical Exhibit
CX	Complainant's Documentary Exhibit
FF	Finding of Fact
RB	Respondents' Brief
RBR	Respondents' Reply Brief
RBPX	Respondents' Physical Exhibit
RBX	Respondents' Documentary Exhibit
SB	Staff's Brief
SBR	Staff's Reply Brief
SPX	Staff's Physical Exhibit
SX	Staff's Documentary Exhibit

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I. Procedural History

On March 16, 1993, complainant Genentech, Inc. (Genentech) filed a complaint. Letters supplementing the complaint were filed on March 30, March 31, April 5, April 6, April 9, April 12, and April 22, 1993. On August 18, 1993 Genentech filed an amended complaint and a motion for temporary relief. (Motion Docket No. 358-1). The complaint, as supplemented and amended, alleged violations of subsection (a)(1)(B) of section 337 in the importation into the United States, the sale for importation, and the sale within the United States after importation of recombinantly produced human growth hormone alleged to be manufactured abroad by processes covered by certain claims of United States Patent Nos. 4,366,246 (the '246 patent), 4,342,832 (the '832 patent), 4,601,980 (the '980 patent), and 5,221,619 (the '619 patent).

The Commission published the notice of investigation on September 29, 1993 naming Novo Nordisk A/S, Novo Nordisk of North America, Inc., Novo Nordisk Pharmaceuticals, Inc., and Zymogenetics (Novo respondents) and Bio-Technology General Corp. and Bio-Technology General (Israel) Ltd. (BTG respondents or BTG). 58 Fed. Reg. 50954-55. Pursuant to Commission interim rule 210.24(e)(8), the Commission also provisionally accepted Genentech's Motion No. 358-1 for temporary relief.

Order No. 7, which issued September 28, 1993 following the filing by the staff of Motion No. 358-4, designated the temporary phase of the investigation more complicated and extended the temporary exclusion order initial determination (TEO ID) due date until January 27, 1994.

By notice dated November 10, 1993, the Commission determined not to review the administrative law judge's initial determination granting a joint motion to terminate the temporary relief phase of the investigation as to the

Novo respondents on the basis of a consent order.

The administrative law judge held an evidentiary hearing on the temporary phase of the investigation from December 13 through December 18, 1993, with complainant, the BTG respondents and the staff represented. Post hearing submissions have been made. On January 10, 1994, commencing at 8:00 am and continuing to 10:30 pm, these were closing arguments.

The matter is now ready for the TEO ID.

The TEO ID is based on the entire record compiled at the TEO hearing and the exhibits admitted into evidence. The administrative law judge has also taken into account his observation of the witnesses who appeared before him during the TEO hearing. Proposed findings submitted by the parties participating at the TEO hearing not herein adopted, in the form submitted or in substance, are rejected either as not supported by the evidence or as involving immaterial matters. The findings of fact of this TEO ID include references to supporting evidentiary items in the record. Such references are intended to serve as guides to the testimony and exhibits supporting the findings of fact of the administrative law judge. They do not necessarily represent complete summaries of the evidence supporting said findings.

II. Jurisdiction

The Commission's in personam jurisdiction over the temporary phase of this investigation is based on the appearance of complainant and the BTG respondents. The Commission has subject matter jurisdiction because the alleged unfair acts and unfair methods involve importation and sale in the United States of recombinantly produced human growth hormone alleged to be manufactured abroad by processes covered by claim 1 of the '832 patent, claim 2 of the '980 patent and claims 1, 10 and 38 of the '619 patent which patents

are the only patents involving the BTG respondents in the temporary phase of the investigation.

BTG has argued that there was no evidence that BTG imported human growth hormone into the United States other than for clinical trials and for basic research and since there has been no act of infringement, Genentech's TEO motion should be denied for lack of jurisdiction (RB at 52). Complainant and the staff argued that the Commission does have jurisdiction over BTG in this investigation.

BTG's contention is rejected. In Amgen Inc. v. U.S.I.T.C., 902 F.2d 1532, 14 USPQ2d 1734, 1736-37 (Fed. Cir. 1990) (Amgen) the Federal Circuit has stated that:

> As is very common in situations where a tribunal's subject matter jurisdiction is based on the same statute which gives rise to the federal right, the jurisdictional requirements of section 337 mesh with the factual requirements necessary to prevail on the merits. In such a situation the Supreme Court has held that the tribunal should assume jurisdiction and treat (and dismiss on, if necessary) the merits of the case.

Id at 1737-38, citing Bell v. Hood, 327 U.S. 678, 682 (1946); Jackson Transit Authority v. Local Division 1285, Amalgamated Transit Union, AFL-CIO-CLC, 457 U.S. 15, 21 (1982); Do-Well Machine Shop v. United States, 870 F.2d 637, 639-49 (Fed. Cir. 1989). Accordingly, the Court reversed a Commission's determination that it lacked jurisdiction and held that the Commission should have "assumed jurisdiction, and, if the facts indicate that Amgen cannot obtain relief . . . the Commission should have dismissed on the merits." Id at 1739. The two exceptions to this general rule, where the claim is "immaterial and is brought solely for the purpose of obtaining jurisdiction in a particular forum" and where the claim is "wholly insubstantial and frivolous," were found not to exist in that case. Id at 1738.

The allegations of complainant in the complaint regarding BTG's importation are found to be neither "immaterial" nor brought solely to obtain jurisdiction in the Commission, nor to be "wholly insubstantial and frivolous." Thus, there is substantial support in the record for complainant's allegations. Even BTG admits that it has imported human growth hormone into the United States although it is argued that it was imported only for clinical trials and for basic research.

III. Standard To Be Applied In Issuing Temporary Relief

Under 19 U.S.C. §1337 (e)(3), the analysis in determining whether to grant temporary relief is the same as that which courts within the Federal Circuit use in deciding whether to grant preliminary injunctions. The analysis requires a balancing of four factors:

1. Complainant's probability of success on the merits;

2. Threat of irreparable harm to the domestic industry in the absence of the requested relief;

3. The balance of harm between the parties; and

4. The effect, if any, that issuance of the requested temporary relief would have on the public interest.

Certain Circuit Board Testers, Inv. No. 337-TA-342, Commission Opinion (April 5, 1993) at 4 (Circuit Board Testers). No one factor taken individually is necessarily dispositive. Rather, a weak showing on one factor may be "overborne, by the strength of others." Chrysler Motors Corp. v. Auto Body Panels of Ohio, Inc. 908 F.2d 951, 953 (Fed. Cir. 1990) (Chrysler Motors).

With respect to probability of success on the merits, the Federal Circuit has held several times that, in order to prevail, the movant's probability of success must rise to the level of a reasonable likelihood of success. Roper Corp. v. Litton Systems, Inc., 757 F.2d 1266, 1271 (Fed. Cir.

1985) (Roper); H.H. Robertson Co. v. United Steel Deck, Inc., 820 F.2d 384, 388 (Fed. Cir. 1987) (H.H. Robertson); T.J. Smith and Nephew Limited v. Consolidated Medical Equipment, 821 F.2d 646, 647 (Fed. Cir. 1987) (T. J. Smith). Moreover, the Federal Circuit has held that if an accused infringer chooses not to challenge validity and so fails to carry its burden to show that a patent is invalid, the court must treat the movant's probability of success on the issue of validity as having been established. Roper, 757 F.2d at 1270.

Federal courts have considered the following factors, inter alia, relevant, either in finding that a presumption of irreparable harm has been rebutted or in assessing, upon a factual showing, whether a patentee would be irreparably harmed in the absence of temporary relief:

> 1. Whether the patent owner has delayed in bringing action against the accused infringer T. J. Smith, 821 F.2d at 648;
>
> 2. Whether the patent owner has granted licenses. The grant of licenses has been held incompatible with the emphasis on the right to exclude Id.;
>
> 3. Whether the accused infringer has stopped infringing Roper, 757 F.2d at 1272;
>
> 4. Whether the denial of a preliminary injunction would have a negative effect on the patent owner's market share. Lubrizol Corp. v. Exxon Corp., 7 USPQ2d 1573, 1528 (N.D. Ohio 1988);
>
> 5. Whether, in the absence of preliminary relief, other potential infringers will be encouraged to infringe. Hybritech Inc. v. Abbott Laboraties, 847 F.2d 1446, 1456 (Fed. Cir. 1988) (Hybritech);
>
> 6. Whether the patent involves rapidly changing technology and a short life cycle product, so that the patent may not be of value when the litigation is finished Id.; and
>
> 7. Whether the potential injury to the patent owner is unpredictable Id.

Certain Pressure Transmitters, Inv.No. 337-TA-304, USITC Pub. 2392, Commission

Opinion Temporary Relief (March 19, 1990) at 8, aff'd sub nom. Rosemount, Inc. v. USITC, 910 F.2d 819 (Fed. Cir. 1990) (Pressure Transmitters), citing T.J. Smith, 821 F.2d at 647; Roper, 757 F.2d at 1271; Lubrizol Corp. v. Exxon Corp., 7 USPQ2d 1513 (N.D. Ohio 1988); Hybritech, 849 F.2d at 1456. In addition, although the Federal Circuit has held that money damages are not the sole remedy against infringement, Atlas Powder Company v. Ireco Chemicals, 773 F.2d 1230, 1233 (Fed. Cir. 1985), the Supreme Court has held that "[t]he possibility that adequate compensatory or other corrective relief will be available at a later date, in the ordinary course of litigation, weighs heavily against a claim of irreparable harm." Sampson v. Murray, 415 U.S. 61, 90 (1974), quoting Virginia Petroleum Jobbers Ass'n v. FPC, 259 F.2d 921, 925 (D.C. Cir. 1958).

Although Smith International, Inc. v. Hughes Tool Co., 718 F.2d 1573 (Fed. Cir. 1983) (Smith International) held that the court should take into account, when relevant, the possibility of harm to other interested persons from the grant or denial of the injunction and the public interest, Id. at 1579, the Federal Circuit has not found it necessary to consider those equitable factors if the movant fails to establish that it will suffer irreparable harm in the absence of relief. Roper, 757 F.2d at 1579. On the other hand, the Federal Circuit has held that even when irreparable injury is presumed and not rebutted, it is still necessary to consider the balance of hardships between the parties before an injunction may be issued. H. H. Robertson, 820 F.2d at 390.

IV. Parties

A. Identification

See FF 1, 2 for identification of private parties.

B. Positions of the Parties

Complainant argued that a balancing of the equities substantially favors complainant in this TEO proceeding. It argued that it has established a very strong likelihood of success on the merits because its three "pioneering patents" are valid and enforceable, and the methods practiced by BTG are clearly covered by the three patents. It is argued that complainant has expended huge sums in developing the technology and establishing the U.S. industry and market; that absent timely temporary relief, complainant's U.S. industry will suffer irreparable harm from BTG's unfair market entry; that BTG can survive with the imposition of temporary relief; and that the public interest would be served by the grant of temporary relief (CB at 82-92).

BTG argued that complainant cannot demonstrate with reasonable certainty that any single market factor could harm complainant, especially not the entry of a small unknown company like BTG, and that complainant's theory of injury is predicated upon a series of assumptions that are unsupported by the evidence in this investigation. It is also argued that the evidence adduced at the hearing establishes that complainant is unlikely to prevail in defending the claims of the '832, '980 and '619 patents in issue against charges that the three patents are invalid, unenforceable and not infringed by BTG and that the record evidence indicates that complainant's domestic industry allegations are principally based on a manufacturing process that appears markedly different from that which is covered by the three patents-in-issue. It is further argued that the facts show that the balance of harm to the parties tips in favor of BTG and that the record evidence shows that denial of complainant's Motion No. 358-1 for temporary relief would not be contrary to the public interest (RB at 6-14).

The staff at closing argument argued that the standard in the TEO proceeding is irreparable harm; that the polar opposite of irreparable harm would have to be a respondent that is not even competing; and that the next closest thing to the polar opposite of irreparable harm is the situation where a respondent is legally barred from competing in the United States market. It argued that it is the latter situation which "we have right now," and the "situation we have when this temporary relief proceeding is over." In closing argument the staff stressed that BTG has not made any sales in the United States market and there is no competition at this time and there will be no competition at the conclusion of the Commission's consideration of the temporary relief motion (Tr. at 2996-97).

The staff in its initial posthearing brief argued that based on the evidence admitted at the temporary relief hearing, it is the staff's view that complainant will likely succeed on the merits on the issues of validity and enforceability of all of the claims at issue; that with respect to infringement, complainant will likely prove its case as to claim 2 of the '980 patent, claim 1 of the '832 patent and claims 1 and 38 of the '619 patent and will not succeed as to claim 10 of the '619 patent; that complainant probably will succeed as to domestic industry; that as to claim 2 of the '980 patent and claim 1 of the '832 patent, complainant's probability of success on the merits is quite high, possibly enough to justify a presumption of irreparable harm, although it does not matter whether or not a presumption of harm is accorded complainant in view of the lack of actual harm complainant would suffer if the temporary relief were denied (SB at 54-55). Thus the staff argued that the presumption of irreparable harm "can be overcome by clear and convincing evidence to the contrary," citing Pressure Transmitters at 32, and

that the evidence has shown that complainant will not be irreparably harmed in the absence of temporary relief, regardless of whether the presumption of harm applies (SB at 55-56). The staff also argued that in terms of balancing the minimal harm (if any) to complainant if temporary relief is not granted and the moderate harm to BTG if temporary relief is granted, the staff argued that the scales clearly tip in favor of the respondents, indicating that temporary relief should be denied (SB at 60-61). The staff also argued that the dominant public interest factor in this investigation is the public interest in enforcing valid patent rights and this factor favors issuing temporary relief although temporary relief should not be granted because complainant will not suffer any significant harm if such relief is denied (SB at 62-63). The staff concluded that it is clear that where there appears to be a lack of irreparable harm, a likelihood of success will not tilt the balance in favor of temporary relief, and inasmuch as the evidence indicates that complainant will not suffer irreparable harm in the absence of temporary relief, Motion No. 358-1 for temporary relief should be denied (SB at 63).

V. Products Involved

See FF 3, 4.

VI. Importation

The administrative law judge finds that BTG has imported human growth hormone into the United States (See FF 218-243).

VII. Technical Issues[1]

A. Technology Relating To The Technical Subject Matter In Issue

The technology and the vocabulary underlying the technical subject matter in issue should be known to a person of ordinary skill in the art (FF 86). However, to those not versed in molecular biology, said technology, especially the vocabulary used therein, may be unfamiliar. Hence, before the administrative law judge analyzes and decides the technical issues, some insight into the technology and explanation of its vocabulary, as well as general comments relating to the inventions in issue, are essential.

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[1] BTG argued that where a court finds that the movant has clearly not demonstrated irreparable harm (a threshold question in granting temporary relief) temporary relief has been denied, without detailed discussion of the remaining factors of likelihood of success on the merits, balancing of harms and the public interest, citing Webstone Co., Inc. V. Saljack Indus., Inc., 217 USPQ (BNA) LEXIS 1011 (D. Mass. 1982) (Objection No. 26). It also argued that where a court finds that there are important questions of fact which cannot be resolved at the preliminary stage, temporary relief has been denied without discussion of the reminding three factors, citing Gantter v. Unit Venetian Blind Supply Corp., 87 F. Supp. 338, 339 (S.D.Cal. 1949). Accordingly BTG argued where "as here" it is clear that complainant has failed to meet the burden of proof as to the threshold element of immediate and substantial harm, the administrative law judge need not resolve the complicated issues presented with respect to validity and infringement, the public interest, and the balance of harms in this investigation in order to deny temporary relief. (RB at 2).

Complainant argued that BTG wants the administrative law judge to ignore not only the relevant Commission interim rules 210.24(e)(17)(i) and 210.24 (e)(1) and (9) but also the relatively recent directives from the Federal Circuit in Pretty Punch Shoppettes, Inc. v. Hauk, 844 F. 2d 782 (Fed, Cir. 1988), Black & Decker, Inc. v. Hoover Service Center, 886 F. 2d 1285, 1286 (Fed, Cir, 1989), and Epic Metals Corp. v. H. H. Robertson Co., 870 F. 2d 1574, 1577 (Fed, Cir. 1989) which squarely require the contrary, even if the Commission were to determine that a temporary exclusion order should not issue in a given factual situation (CBR 16, 17). The staff argued that the Commission rules contemplate that the initial determination in this TEO proceeding give the Commission an opinion on all issues (Tr at 3032).

A review of the authorities cited by complainant convinces the administrative law judge that he cannot ignore, in this initial determination, any of the four factors enumerated by the Commission in Circuit Board Testers.

The material "human growth hormone" is sometimes referred to as "hGH" (FF 13). Human growth hormone is a protein which controls cellular growth (FF 29). A protein is an agent which either makes up the cells' structure or which performs its activities. To the latter category of proteins belong enzymes such as hormones (FF 32).

Proteins are composed of linear sequences of amino acids. The information for the linear sequence of amino acids in hGH is encoded by the linear sequence of nucleic acids in the hGH DNA (FF 36). Thus the order in which the amino acids in proteins are strung together define all of the known proteins. In general, the particular sequence of amino acids in a protein defines the identity and the chemical characteristics of that protein, although the way the protein folds contributes to the characteristics of said protein[2] (FF 122-124). The amino acids are lined together by means of covalent bonds, called peptide bonds. Thus, proteins are called "peptides"[3] or "polypeptides." Like DNA, the proteins have different ends. One end (the beginning) is called the "amino-terminal" or ("N-terminal") end, and the other end is called the "carboxyl-terminal" or ("C-terminal") end. Some proteins

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[2] Folding in the human growth hormone molecule, which results in a three-dimensional globular structure is attributed, in part, to the formation of a chemical bond, referred to as a disulfide covalent bond, between specific amino acid residues (cysteine residues) within the chain of human growth hormone amino acids. That disulfide bond causes the protein to fold back on itself and consequently to give the molecule the three dimensional structure (FF 131 to 133). In the human growth hormone protein obtained from the pituitary glands of human cadaver, it is the way that the human growth folds and the particular sequence of 191 amino acids that makes the protein human growth hormone. Significantly, the information for folding is in the primary sequence of a protein which is represented by the unfolded precursor (FF 122, 126).

[3] A peptide is a compound containing two or more amino acids in which the carboxyl group of one acid is linked to the amino group of another acid (FF 9).

are secreted out of the cell and this process can require an amino acid sequence called a "leader sequence." By this process -- called "secretion" -- the protein is moved from inside the cell to outside the cell (FF 36).

The function of human growth hormone can be understood by considering the results of a growth hormone deficiency -- dwarfism. Initially, hGH was obtained from human cadavers. Pituitary glands were isolated, the hGH was obtained from certain cells of the glands by a laborious extraction, and injected into people (FF 40). There never was enough to fulfill the need and the consequent scarcity of the substance coming only from human cadavers limited its applications to the treatment of hypopituitary dwarfism, and even so limited, reliable estimates had suggested that human-derived hGH was available in sufficient quantity to serve not more than about 50% of afflicted subjects (FF 59). Moreover, it was also noticed that individuals treated with the cadaver-derived hGH were at risk for a disease called Creutzfeld-Jakob disease that attacked the brain and was fatal. This disease was caused by an infectious agent in the hGH derived from cadavers. It was for that reason that the FDA banned hGH (FF 40). Human growth hormone as it was obtained from the pituitary glands consisted of 191 amino acids and had a molecular weight of about 21,500 (FF 59).

A cell is the basic unit of a living organism. Some organisms consist of only one cell -- for example, a microbial cell like Escherichia coli (E. coli). Other organisms are composed of many cells, for example, a human. In multi-cellular organisms, there are different types of cells which differ in their function(s). Every human cell has nucleus which contains the information necessary for directing the cell's activities. This information is contained in a long, double stranded molecule called DNA (FF 31, 41, 42),

and a cell has the necessary and complex machinery required to synthesize proteins from DNA (FF 32).

DNA (deoxyribonucleic acid) is a polymer whose individual units are four "nucleic acids" (or "nucleotides") called adenine (A), thymine (T), cytosine (C), and guanine (G). Those nucleic acids are linked together in a DNA strand. The beginning of the strand is called the "5' end" and the end of the strand is called the "3' end." Human chromosomes are composed of DNA. It is the DNA molecule that is inherited from generation to generation (FF 31). It is significant that in the late 1970's, and even today, there were no restrictive endonucleases or other enzymes or chemicals available to cut DNA anywhere at will (FF 188).

To synthesize a polypeptide protein, there is first the synthesis of a intermediate called "messenger RNA" (mRNA), which like DNA is a long linear molecule, but which is single stranded. Also like DNA, RNA is a polymer and has 5' and 3' ends. The individual units of RNA are the "ribonucleotides" -- adenine (A), uracil (U), cytosine (C), and guanine (G). Uracil serves in RNA as thymine serves in DNA (FF 32). The process of messenger RNA (or mRNA) synthesis is called "transcription" (FF 33). Messenger RNA, once produced, is transported from the nucleus to the cytoplasm where it associates with "ribosomes," particles within the cells. At the ribosomes, the information encoded in the mRNA is translated into the amino acid sequence of a protein like human growth hormone, which process is called "translation" (FF 34). The term "expression" is the combined processes of transcription and translation and is the "decoding" of the DNA sequence into a protein sequence (FF 35). Thus the "expression" of encoded information to form a polypeptide involves a two-part process. According to the dictates of certain control regions

("regulons") in the gene,[4] RNA polymerase may be caused to move along the coding strand, forming messenger RNA (ribonucleic acid) in the process called "transcription." In the subsequent "translation" step the cell's ribosomes, in conjunction with transfer RNA, convert the mRNA "message" into polypeptide. Included in the information mRNA transcribes from DNA are signals for the start and termination of ribosomal translation, as well as the identity and sequence of the amino acids which make up the polypeptide. The DNA coding strand comprises long sequences of nucleotide triplets called "codons" because the characteristic bases of the nucleotides in each triplet or codon encode specific bits of information (FF 19). Three nucleotides read as ATG (adenine-thymine-guanine) can result in an mRNA signal interpreted as "start translation", while termination codons TAG, TAA and TGA can be interpreted as "stop translation." Between the start and stop codons lie the so-called structural gene, whose codons define the amino acid sequence ultimately translated. That definition proceeds according to the well-established "genetic code" which describes the codons for the various amino acids (FF 20).

Putting it another way, DNA carries information for individual proteins. Part of DNA is the actual protein-encoding sequence called the "structural gene". The remaining DNA is a sequence necessary for production of the protein called a control sequence or "control region". The first step of

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[4] A "gene" is the basic unit of inheritance. The basic and universal chemical constituent of the gene is deoxyribonucleic acid (DNA). The definition, however, of "gene" can vary and there is no general agreement as to the exact usage of the term, since several criteria that have been used for its definition have been shown not to be equivalent (FF 18). A most common definition of a "gene" is a DNA sequence encoding a single protein. For example, one gene is for human growth hormone, another for insulin. In a human cell, the "nucleus" is in the center of the cell and, within that nucleus, are "chromosomes". Those chromosomes are large pieces of DNA that include individual genes linked together (FF 37).

protein synthesis uses one of those control region sequences -- the "promotor," which is recognized by a component of the cellular machinery called "RNA polymerase," that synthesizes the mRNA. As the RNA polymerase moves along the DNA strand, the mRNA building blocks -- termed "ribonucleotides" -- are assembled into an mRNA strand in the process referred to as transcription. The product of transcription -- the mRNA -- is a faithful copy of one of the two strands of DNA. After its completion, the mRNA moves from one cellular compartment, the nucleus, to another cellular compartment, the cytoplasm, where it associates with another component of the cellular machinery called a "ribosome." The ribosome associates with the mRNA at a specific site, the "ribosome binding site". In bacteria, that sequence is called the Shine-Delgarno sequence (after its discovers). The ribosome moves along the mRNA, and the information encoded in the mRNA is translated into amino acids. By the translation process said amino acids are linked together through "peptide bonds" to produce the protein. Because the ribosome moves in one direction on the mRNA, a convention has developed to described the location of sequences. For example, with respect to the ribosome-binding site, the structural gene to the translated is "downstream" (FF 41).

As already indicated, the information in DNA and its faithful transcript, mRNA, is in the form of three nucleic acid sequences called "triplet codons." Each triplet codon directs the cell to add a particular amino acid to a growing protein chain. The amino acid added is dictated by the cells "decoding" of the genetic code. Proteins are always initiated at a particular codon -- AUG in the mRNA (or ATG in the DNA). This codon encodes

the amino acid methionine (or met)[5]. Once a protein is initiated at the AUG (ATG) codon, the sequence of nucleic acids in mRNA are read in threes (i.e., triplet codons), and the step-wise reading of the codons is referred to as being "in-phase". If there is a shift in the "reading phase," a whole different sequence of amino acids is incorporated into the protein. A shift in reading phase produces an entirely different product, Tyr-Val-Pro-Asn-Try (FF 42).

A cloning vehicle can be a non-chromosomal double stranded DNA comprising an intact "replicon" such that the vehicle is replicated, when placed within a unicellular organism ("microbe") by the process of "transformation." An organism so transformed is called a "transformant" (FF 26). A "plasmid" can be a cloning vehicle derived from viruses or bacteria, the latter being "bacterial plasmids" (FF 27). The term "chemical synthesis" is one method for building a DNA chain. It involves linking the nucleic acids of the DNA chain together, one by one. Today, chemical DNA synthesis can be done by machine. In 1977, it was done by hand in the laboratory (FF 44). An "operon" is a gene comprising structural gen(s) for polypeptide expression and the control region ("regulon") which regulates that expression (FF 21). A "promoter" is a gene within the regulon to which the RNA polymerase must bind for initiation of transcription (FF 22). An "inducer" is a substance which deactivates repressor protein, freeing the operator and permitting RNA

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[5] Met-hGH is a polypeptide which is one hundred and ninety-two amino acids long and has an additional methionine residue at the N-terminus of the sequence of human growth hormone. Met-hGH expressed in E. coli in quantity is biologically inactive, insoluble, improperly folded, and reduced (i.e. lacks the disulfide bonds folded for biological activity). Met-hGH can be rendered biologically active, soluble, properly folded, non-reduced (i.e. disulfide bonds present) by procedures carried out outside E. coli (FF 106, 107).

polymerase to bind to promoter and commence transcription (FF 23). A "catabolite activator protein" ("CAP") binding sinate is a gene which binds cyclic adenosine monophosphate ("c AMP") - mediated CAP, also commonly required for initiation of transcription. The CAP binding site may in particular cases be unnecessary (FF 24). A promoter-operator system, is an operable control region of an operon, with or without respect to its inclusion of a CAP binding site or capacity to code for repressor protein expression (FF 25). The term "complementarily" is a property conferred by the base sequences of single strand DNA which permits the formation of double stranded DNA through hydrogen bonding between complementary bases on the respective strands. Adenine (A) complements thymine (T), while guanine (G) complements cytosine (C) (FF 28).

Microbial derives from the word "microbe," a group of organisms which can only be seen with a microscope. The title of the '619 patent refers to the fact that a microbial cell, not a human cell, is used to express a polypeptide. In the '619 patent complainant first produces a gene for the polypeptide. Because the genetic code is essentially the same in all organisms, including mammals and microbes, that gene can be potentially transcribed and translated -- expressed -- in a microbial cell. Said gene is inserted ("ligated") into a carrier DNA molecule (a cloning vehicle with a reasoned being a common cloning vehicle). The cloning vehicle with its inserted human growth gene can be introduced into a microbial cell (a process called "transformation" of the cell). If the gene is situated in the correct relationship with regard to sequences for expression, a microbial cell will produce the human growth hormone sequences (FF 38). Human growth hormone is not produced by microbes unless the microbes are engineered (i.e.,

transformed) to provide an essential precursor because the microbial cell lacks the human growth hormone gene and hence is incapable of producing hGH which human pituitary cells are able to do (FF 39).[6]

Advances in biochemistry in "recent years", as that term was used on November 8, 1977 (the filing date of the original application for the '619 patent), led to the construction of "recombinant" cloning vehicles in which, for example, plasmids were made to contain exogenous DNA. In particular instances, the recombinant could include "heterologous" DNA, by which is meant DNA that codes for polypeptides ordinarily not produced by the organism susceptible to transformation by the recombinant vehicle. Thus, plasmids were cleaved to provide linear DNA having ligatable termini. Those were bound to an exogenous gene having ligatable termini to provide a biologically functional moiety with an intact replicon and a desired phenotypical property. The recombinant moiety was inserted into a microorganism by transformation and tranformants were isolated and cloned, with the object of obtaining large populations capable of expressing the new genetic information (FF 44).

A variety of techniques, as of November 8, 1977, were available for DNA

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[6] A properly folded, soluble disulfide linked protein molecule of 191 amino acids secreted in the human pituitary can not exist inside a human cell nor can it exist inside a bacterial cell (FF 127). Thus when a molecule of what will become human growth hormone is expressed within a cell in the human body it is expressed with a leader sequence which molecule with the leader sequence inside the cell is a different product than what results outside the cell from the expression. It is a different product because the leader sequence is cleaved off as the molecule is making its way out of the human cell (FF 77, 119, 120, 121). In other words, in expression, the leader sequences are enzymatically removed, such that the hormone enters the piroplasmic space in its free, bioactive form. Microbe cells cannot be relied upon to perform that function. A reducing atmosphere in the microbe, e.g. E. coli, prevents the formation of disulfide bridges which is necessary for a properly folded disulfide linked protein molecule of either 191 or 192 amino acids (FF 102-104).

recombination, according to which adjoining ends of separate DNA fragments are tailored in one way or another to facilitate ligation, the term "ligation" referring to the formation of phosphodiester bonds between adjoining nucleotides, most often through the agency of the enzyme T4 DNA ligase. Thus blunt ends could be directly ligated. Alternately, fragments containing complementary single strands at their adjoining ends were advantaged by hydrogen bonding which positions the respective ends for subsequent ligation. Such single strands, referred to as cohesive termini, could be formed by the addition of nucleotides to blunt ends using terminal transferase, and sometimes simply by chewing back one strand of a blunt end with an enzyme. Again, and most commonly, resort could be had to restriction endonuclease, which cleave phosphodiester bonds in and around unique sequences of nucleotides of about 4-6 base parts in length (FF 46).

Prior to the filing of the initial '619 patent application on November 8, 1977, despite wide-ranging work in "recent years" (as that term was used in the '619 patent) in recombinant DNA research, few results susceptible to immediate and practical application emerged, which was proven especially so in the case of failed attempts to express polypeptide and the like coded for by "synthetic DNA", whether constructed nucleotide by nucleotide in the conventional fashion or obtained by reverse transcription from isolated mRNA complementary or "cDNA") (FF 47).

B. The '619 Patent

Complainant argued that each of claim 1, 10 and 38 is clearly infringed by BTG (CB at 2). In the staff's view, BTG is likely to be found to infringe each of claims 1 and 38 of the '619 patent but not likely to infringe to be found to infringe claim 10 of said patent (SB at 42). Complainant has the

burden to show that that there is a reasonable likelihood of success in complainant establishing that each of claims 1, 10 and 38 is infringed by BTG. Pressure Transmitters, Commission Opinion on Temporary Relief at 6.

Any analysis of infringement initially requires a proper construction of the claims to determine their scope. Palumbo v. Don-Joy Co., 762 F.2d 969, 974 (Fed. Cir. 1985). As with a claim interpretation for patent infringement, an analysis for patent validity also requires interpretation of the language of claims in issue. In addition a claim must be given the same meaning for the purposes of analyzing each of the validity and infringement issues. White v. Dunbar, 119 U.S. 47, 51 (1886); Senmed Inc. v. Richard-Allen Medical Industries, Inc., 888 F.2d 813, 818, n. 7 (Fed. Cir. 1989); W. L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, cert. denied, 469 U.S. 851 (1984).

Claims must be construed to uphold their validity, if possible. Lewmar Marine, Inc. v. Barient, Inc. 827 F.2d 744, 749 (Fed. Cir. 1987), cert. denied, 484 U.S, 1007 (1988). The words of a claim are given their ordinary and accustomed meaning unless it appears from the specification and prosecution history that the inventor intended a different meaning. Smithkline Diagnostics, Inc. v. Helena Laboratories Corp., 859 F.2d 878, 992 (Fed. Cir. 1988); Envirotech Corp. v. Al George, Inc., 730 F.2d 753, 759 (Fed. Cir. 1984). A claim should be construed as it would be by one skilled in the art. Loctite Corp. v. Ultrasel Lit., 781 F.2d 861, 867 (Fed. Cir. 1985). When an inventor chooses to give terms of a claim uncommon meanings, those uncommon definitions must be explained within the patent disclosure and without regard to the accused process. See Intellicall, Inc. v. Phonometrics, Inc., 952 F.2d 1384, 1388 (Fed. Cir. 1992); SRI Int'l v. Matsushita Elec. Corp of Am., 775

F.2d 1107, 1118 (Fed. Cir. 1985).

If parties dispute the meaning of critical claim language, a court may rely on extrinsic evidence, including testimony of witnesses as well as the specification, the prosecution history, prior art and other claims. Tandon Corp. v. United States Int'l Trade Comm'n, 831 F.2d 1017, 1021 (Fed. Cir. 1987). The specification may be used to interpret what the patentee meant by words or phrases in claims, but the claims, not the specification, determine the scope of the invention. E. I. duPont de Nemours & Co. v. Phillips Petroleum Co., 849 F.2d 1430, 1433 (Fed. Cir. 1988). Reference to a preferred embodiment in a specification is not a claim limitation. Laitram Corp. v. Cambridge Wire Cloth Co., 863 F.2d 855, 865 (Fed. Cir. 1988), cert. denied, 490 U.S. 1068 (1989). Under the doctrine of claim differentiation, the presence of an express limitation in one claim negates an intent to limit similarly be implication a claim in which the limitation is not expressed. Kalman v. Limberly-Clark Corp., 713 F.2d 760, 770 (Fed, Cir. 1983), cert. denied, 465 U.S. 1026 (1984).

For the purposes of this TEO proceeding the administrative law judge finds that it is necessary only to interpret the breadth to be given to the terms "preselected functional mammalian polypeptide," and "polypeptide intermediate therefor" recited in generic claim 1 (FF 5), the term "mammalian polypeptide" recited in claim 10 (FF 5) and the term "human growth hormone" recited in dependent claim 38 (FF 5).

1. Claim Interpretation

The initial application for the '619 patent was filed on November 8, 1977. Next a continuation-in-part application was filed, followed by the filing of five continuation applications, the last of which was filed on

January 15, 1992 and issued as the '619 patent (FF 8, 10).

At closing argument when the administrative law judge asked complainant's counsel to relate the stated summary of the invention (FF 11) to claim 1 in issue (FF 5), complainant's counsel stated that said summary is broad (Tr. at 2551). BTG's position was that said summary is not a summary of the invention claimed in generic claim 1, but rather is directed to some other invention relating to a cloning vehicle (Tr. at 2550, 51). It is a fact that the summary states that the invention provides a recombinant plasmid suited for transformation of a bacterial host and use therein as a cloning vehicle (FF 11). The summary states nothing about the production of a polypeptide "comprising a preselected functional mammalian polypeptide or polypeptide intermediate therefor" as recited in claim 1 (FF 5) nor a process for production of a human growth hormone as recited in claim 38. Under the subheading "Background", the '619 patent does state that in "this application" the inventors describe what appears to represent the first expression of a functional polypeptide product, viz. somatostatin, from a synthetic gene "together with related developments which promise widespread application" (FF 48). Also there is a later statement in the '619 patent that the "techniques" discussed are applicable to the production of mammalian hormones or intermediates therefor and human growth hormone is listed (FF 58). However, the '619 patent contains no experimental examples of the production of human growth hormone or processors of such hormone.

While the terms "mammalian hormones or intermediates therefor" as well as "human growth hormone" are found in the specification of the '619 patent (FF 58), a review of the specification does not show that those terms are defined in the '619 patent and no party has relied on the '619 prosecution

history for definition of those terms.

The only specific experimental examples in the '619 patent are for the making of somatostatin and of insulin (FF 12). Each of somatostatin and insulin is a fusion protein (FF 15). Somatostatin is also a functional mammalian polypeptide (FF 16). Significantly neither somatostatin nor insulin is a human growth hormone (FF 15).

It was known in the late seventies that human growth hormone secreted in the human pituitary consists of 191 amino acids and has a molecular weight of about 21,500 (FF 61). Such human growth hormone is more than three times as large as insulin (FF 59). While such human growth hormone consists of 191 amino acids, the molecular formula for somatostatin (FF 14) shows that it has a relatively low molecular weight consisting of a mere fourteen (14) amino acids (FF 17).

The experimental section of the '619 patent discloses that substantially pure somatostatin may be obtained (FF 56). To obtain that substantially pure somatostatin involved were "construction of somatostatin gene fragments," "ligation and acrylamide gel analysis of somatostatin DNA," "construction of recombinant plasmids", "radioimmune assay for somatostatin activity" and purification (FF 49-55). Even with the low molecular weight of somatostatin, the '619 patent shows that a construction of a certain plasmid did not provide for detection of somatostatin (FF 53). Critical to the formation of somatostatin is a formic acid-cyanogen bromide treatment followed by standing for 24 hours at room temperature and diluting ten fold with water (FF 55).

The '619 patent discloses that a synthetic gene approach was used to actually express the proteins somatostatin and insulin. In the case of somatostatin, there is expert testimony that this synthetic gene approach

involved introducing a synthesized somatostatin gene into the bacterial host cell by inserting the gene into a plasmid containing a number of natural bacterial genes, including a fragment of the gene for a protein called beta-galactosidase and producing a "fused" beta galactosidase/somatostatin gene which would produce a hybrid beta-galactosidase/somatostatin protein (FF 57).

While the synthetic gene approach was useful to produce the low molecular weight somatostatin and insulin, in the case of far larger protein products such as human growth hormone, whose gene is correspondingly more complex and less susceptible to facile synthesis, as of November 8, 1977 which is the initial filing date of the '619 patent, as well as after November 8, 1977 scientists working in the field stated that there were real difficulties in producing such larger proteins (FF 73).

The administrative law judge finds that it is a fact that despite the statements in the '619 patent that "this application" concerns "related developments which promise wide spread application" (FF 48) and that the techniques discussed in the '619 application are applicable to the production of mammalian hormones or intermediates therefor and human growth hormone is listed (FF 58), as of the November 8, 1977 initial filing date of the '619 patent human growth hormone could be obtained only by the laborious extraction from the pituitary glands of human cadavers, and it was not until at least the invention in the '980 patent was made by inventors different from the named inventors on the '619 patent, which '980 patent has an initial filing date of July 5, 1979, that human growth hormone could be obtained by a process other than the laborious extraction from pituitary glands (FF 66). Complainant's counsel has even admitted that a person of ordinary skill in the art (FF 86) could not from the '619 patent make a human growth hormone if one did not have

the leader sequence, and that the '619 patent says nothing about the leader sequence, and the '619 patent does not enable such a person to get rid of the leader sequence (FF 60, 62, 64-65, 67-68).

In addition, after the initial November 8, 1977 filing date of the '619 patent the same scientists working in the field stated that while workers have attempted to express genes derived not by organic synthesis but rather by reverse transcription form the corresponding messenger RNA purified from tissue, two problems have attended this approach. Thus reverse transcriptase may stop transcription from mRNA short of completing cDNA for the entire amino acid sequence desired. Also, those scientists have stated that reverse transcription of mRNA for polypeptides that are expressed in precursor form has yielded cDNA for the precursor form rather than the bioactive protein that results when, in a eukaryotic cell, leader sequences are enzymatically removed; that thus far no bacterial cell has been shown to share the capability of removing leader sequences so that mRNA transcripts have yielded expression products containing leader sequences of the precursor form rather than the bioactive protein itself (FF 75). Also, the same scientists stated, after November 8, 1977, that past attempts by others to bacterially express hormones or their precursors from mRNA transcripts have on occasion led only to the production of conjugated proteins not apparently amendable to extracellular cleavage (FF 75).

The record demonstrates that a leader sequence is an amino-terminal sequence that is required for the secretion of the growth hormone in humans; that this so-called leader sequence is not part of the final growth hormone product produced from the pituitary glands because it is removed by human cells (FF 77). The record shows that polypeptide hormones are expressed in

precursor form with leader sequences of protein involved, e.g. in transport to the human cellular membranes. Thus in expression from eukaryotic human cells, those sequences are enzymatically removed such that the hormone enters the periplasmic space in its free, bioactive form. Hence, the leader sequence exits in nature to help the protein emerge from the human cell after expression and is clipped off automatically as the protein leaves the mammalian cell. Unfortunately, microbial cells cannot be relied upon to perform the clip off function. In the seventies it was desirable to remove sequences coding for such leader sequences from an RNA transcript for production of human growth hormone involving expression from microbial cells (FF 119-121, 184). In other words, while the leader sequence is removed when growth hormone is expressed in a mammalian cell, the sequence is not removed when the hormone is expressed in the microbial cell, such as E. coli. Just how to express a protein in a microbial cell without this leader sequence was a problem that plagued the scientific community after the initial November 8, 1977 filing date of the '619 patent. For example, in an August 1978 scientific meeting, the leading scientist from the University of California, Howard Goodman, when asked how he would remove the leader sequence from an expressed growth hormone answered that he had "very few ideas." Goodman didn't even think that the leader sequence necessarily had to be removed from the expressed growth hormone because Goodman told the audience "The question is whether it is ever going to be really necessary to take the hormone out of the fused protein" (FF 77).[7]

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[7] Complainant represented that one could not from the '619 patent make a human growth hormone if one did not have the leader sequence on it (FF 69). The '619 patent however does not disclose making human growth hormone with a leader sequence on it. Moreover, complainant admitted that the prior art was (continued...)

It is a fact that the '619 patent had examples directed to the production of somatostatin and insulin. Somatostatin however has a relatively low molecular weight (FF 14, 17) and insulin is less than one third as large as human growth hormone (FF 59). Complainant in fact has admitted that genes as long as that for human growth hormone, i.e. 191 amino acids, and then three times that many, or 573 codons, were too long to synthesize as of the initial November 8, 1977 filing date of the '619 patent (FF 60).

At closing argument the staff admitted that the chemical synthesis of 191 codon gene was an enormous engineering feat and a monumental task in the industry (FF 72). The staff, however, argued that it did not agree that the '619 patent would not necessarily enable one skilled in the art to produce human growth hormone because the '619 patent "gives you the means." In light of admissions by complainant and the statements of leading scientists in the field and persons who are considered to have skills beyond one of ordinary skill in the art[8], the administrative law judge rejects the staff's argument.

Based on the forgoing the administrative law judge finds that it is not reasonably likely that complainant, despite certain language in the '619 specification (FF 58), will be able to establish that the term "preselected functional mammalian polypeptide" of claim 1 of the '619 patent and the term "mammalian polypeptide" of claim 10 of said patent include "human growth

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[7](...continued)
able to get human growth hormone with the leader sequence (FF 71). In any event leader sequence-containing proteins are nonfunctional (FF 77(a)).

[8] Seeburg et. al., working in the laboratory of Howard Goodman, who for years worked with growth hormone-encoding DNA sequences, were unable to produce functional rat growth hormone because they had no way to get rid of the inactivating leader encoding sequence which accompanied their cDNA (FF 150). Goodman had in 1978 "very few good ideas" about removing the leader sequence from an expressed growth hormone (FF 77).

hormone," although complainant can establish that the term does include low molecular weight materials illustrated for example by somatostatin and human insulin. Moreover the administrative law judge finds that while the term "polypeptide intermediate therefor" of claim 1 of the '619 patent may read on any fused protein gene involving the production of low molecular weight mammalian polypeptides (FF 57, 137), it is not reasonably likely that complainant will be able to establish that "polypeptide intermediate thereof" includes any human growth hormone precursor. Also based on the lack of any definition of "human growth hormone" in the '619 patent and the knowledge of human growth hormone, as it is secreted from the human pituitary gland (FF 61), the administrative law judge finds that it is not reasonably likely that complainant will be able to establish that the term "human growth hormone," as it is used in the '619 patent, covers anything other than a compound consisting of 191 amino acids and having a molecular weight of about 21,500.

2. Validity of Claims 1, 10 and 38 Under 35 U.S.C. § 103

BTG argued that claim 1 of the '619 patent defines an alleged invention which was obvious at the time it was allegedly made to those of ordinary skill in the art over Struhl et al (1976) (FF 87) alone, and an Itakura et al abstract (1977) (FF 88) alone, or in combination; that to a person of any skill in the art, it would have been obvious in November 1977 how to make a functional mammalian polypeptide; that the Struhl et al reference discloses expression of a functional polypeptide in a microbial cell culture and the use of an expression control region homologous to the microorganism; that the Itakura et al abstract, which discloses the entire claimed invention, is prior art under 35 U.S.C. § 102(a); and that there is no credible evidence showing any conception or reduction to practice by the inventors prior to the

publication of the abstract (RB at 79-80).

Complainant argued that Struhl discloses using a yeast control region to express a yeast gene and thus involves neither a mammalian gene nor a homologous control region. It is argued that the Itakura abstract is not even prior art, being a publication of the inventor's own work only two months before the '619 effective filing date of November 8, 1977 and after reduction to practice of the '619 invention (CB at 12, 13).

The staff argued that the Struhl reference discloses a method for expression of certain yeast DNA; that it does not describe a method for expression of a mammalian polypeptide in an E. coli cell under the control of an expression control region homologous to the E. coli cell; and that in view of the differences between Struhl and the claims of the '619 patent and in view of the widespread acclaim of the invention disclosed in the '619 patent, it is the staff's position that BTG's obviousness defense on Struhl will in all likelihood fail (SB at 35).

The staff also argued that there is no credible evidence indicating that the Itakura reference is prior art as to the '619 patent; and that the evidence of record indicates that the invention of the '619 patent was reduced to practice prior to the publication of the Itakura reference (SB at 35-36).

The administrative law judge finds that the evidence of record does indicate that the invention of the '619 patent was reduced to practice prior to the publication of the Itakura reference (FF 89). Moreover, there is expert testimony that Struhl concerned a polypeptide from a unicellular organism, a yeast cell, which is very different from a mammal (FF 87). Accordingly the administrative law judge finds that BTG is not likely to establish that claims, 1, 10 and 38 the '619 patent is not valid under 35

U.S.C. § 103.

3. Validity of Claim 38 Under 35 U.S.C § 112

BTG argued that claim 38 of the '619 patent is invalid under 35 U.S.C § 112 because the patent does not disclose any method of making biologically active human growth hormone (RB at 78).

For the reasons set forth in section VII B 1, supra, involving claim interpretation, the administrative law judge finds that there is a reasonable likelihood of success that BTG will establish that claim 38 of the '619 patent is not valid under the first paragraph of 35 U.S.C § 112.[9]

4. Alleged Infringement of Claims 1 and 10

The accused BTG process is detailed in the findings (see FF 90, 92, 110-114, 116-118). Examination of the accused process convinces the administrative law judge that it is not reasonably likely that complainant will succeed in establishing that BTG infringes either claim 1 or claim 10 of the '619 patent. Thus the administrative law judge finds that complainant will not be able to establish that BTG has a process for the production of a polypeptide comprising a "preselected functional mammalian polypeptide" or "polypeptide intermediate," as those terms in claim 1 have been interpreted by the administrative law judge. He further finds that complainant will not be able to establish that BTG has a process for the production of "mammalian

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[9] The first paragraph of 35 U.S.C. §112 reads:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention. (Emphasis added)

polypeptide" as that term in claim 10 has been interpreted by the administrative law judge.

C. The '980 Patent

Complainant argued that infringement by BTG of claim 2 of the '980 patent is clear (CB at 33). It is argued that BTG has offered a "glossary" in which "human growth hormone" is defined narrowly to include only the active, folded, disulfide-bonded form of a hormone, and without an amino-terminal methionine (met), which narrow definition is inconsistent with the definition used by the inventors of the '980 patent, and is inconsistent with

that the '980 specification even speculates "(wrongly, it turned out)" that after being expressed the met might be removed naturally as the human growth hormone left the cell; that in any event the '980 specification made clear the inventors' intention to cover either alternative; and that consistently with the inventors of the '980 patent,

(CB at 31).

It is also argued by complainant that while BTG argued that expression of human growth hormone must take place during the culturing step, claim 2 of the '980 patent has no such requirement, stating only that there must be culturing of cells having plasmids that "will" express a gene for human growth hormone with no requirement of when that expression must take place. Complainant argued that while BTG seems to argue that the word "said", five words from the end of claim 2, implies that the isolated and purified human growth hormone must be in the same form as when it was expressed, this makes

no sense whatsoever, and would render claim 2 meaningless; that it is the very process of taking the polypeptide out of the cell, into an oxidizing atmosphere, that converts it from inactive to active form; and that were claim 2 of the '980 patent to require preserving inactivity throughout purification it would be of little value, as anyone who obtained active human growth hormone would be excluded from infringing said claim 2. Complainant argued further that BTG plays a word game with the words "unaccompanied by . . . other extraneous protein bound thereto," when BTG argued that such excludes even other proteins that happen to be next to human growth hormone in the cell in inclusion bodies, and temporarily "stuck" to the human growth hormone by hydrophobic interactions or ionic (but not covalent) bonds, which is a complete distortion to what said claim 2 is referring to; and that the entire "unaccompanied" phrase, which includes both the leader sequence and the other extraneous protein, is part of the definition of what the gene is "for," and the "extraneous protein" is thus an exclusion from the expression product of the human growth hormone gene, which involves covalent bonds within the expression amino acid chain, and has nothing whatsoever to do with other proteins, expressed by other genes, that just happen to be "stuck" temporarily to the human growth hormone (CB at 32-33).

BTG argued that it does not infringe claim 2 of the '980 patent; that BTG,

BTG argued that it does not

BTG further argued that its process is not equivalent of claim 2 of the '980 patent in issue; that BTG's process does not perform substantially the same function in substantially the same manner to achieve substantially the same result; and that

BTG has carried out a significantly different process which is not equivalent of said claim 2 process of the '980 patent (RB at 64-65).

The staff argued that BTG practices all of the steps of claim 2 of the

'980 patent as properly construed and thus infringes claim 2 (SB at 39). Thus it argued that it is uncontested that the BTG process for producing human growth hormone involves

The staff concluded that it is probable that it will be determined that BTG practices the claim 2 requirement of

The staff also argued that as that term should be construed in the context of the '980 patent (SB at 37).

The staff further argued that while BTG argues that it does not practice

BTG has not succeeded in establishing that there is a limitation in claim 2 of the '980 patent with respect to

It is also argued by the staff that, in BTG's process,

that while BTG argues that

and that claim 2 is not avoided by the fact that

The staff further argued that BTG's process includes the claimed elements of

It is argued that

The staff argued that the result of the entire BTG process is human growth hormone comprised of the particular sequence of 191 amino acids that corresponds to the sequence of 191 amino acids of human growth hormone derived from a human source which is biologically active and useful for the treatment of hypopituitary dwarfism and that

that step is not excluded from or required by claim 2 of the '980 patent (SB at 38, 39).

Complainant, in reply, argued that nowhere does BTG deal with

While complainant argued that Gottesman is absolutely right about the importance of tertiary polypeptide structure, and is right that recombinantly expressed polypeptides only achieve their tertiary structure outside the cell in which they are expressed, complainant argued that those agreed basic facts highlight BTG's "fundamental theater-of-the-absurd quality" (CBR at 8, 9). It also directed the administrative law judge's attention to Gottesman's use of "met-hGH" in Gottesman's glossary to refer to both the active and inactive forms of the 192 amino acid sequence, which complainant argued is an example of how a semantic defense that is built on an essentially "dishonest foundation" will eventually circle back to contradict itself (CBR at 12).

BTG, in its reply, reiterated its position, that BTG does not infringe claim 2 of the '980 patent because

that complainant concedes that "[a]t its

moment of birth, upon expression, the polypeptide is in an inactive form"; "that the inactive expression product must be properly folded and disulfide bonds formed, but those bonds cannot be present due to the 'reducing chemical environment' of the cell"; that those bonds also cannot be present in insoluble met-hGH, "either inside or outside inclusion bodies"; that the expression product includes proteins; and that since it is undisputed that

BTG does

not practice claim 2 of the '980 patent (RBR at 31).

BTG argued, in its reply, that while complainant and the staff contend that met-human growth hormone "comprises" human growth hormone, because the 191 amino acid sequence of the latter is included within the 192 amino acid sequence of the former, the '980 patent states that human growth hormone "consists of 191 amino acids" and the term "consists of" is closed-ended. It argued further that since

is not human growth hormone, and since the process steps used by BTG are entirely different, there can be no infringement of claim 2 of the '980 patent (RBR at 32, 33).

The staff, in its reply, reiterated its position that while BTG argues that it does not practice the claim 2 process step of "culturing bacterial transformants containing recombinant plasmids which will, in a transformant bacterium, express a gene for human growth hormone" because in its process,

BTG

has not demonstrated that said claim 2 contains any limitation

and in

the staff's view it does not appear likely that BTG will be able to establish that such a limitation should be read into claim 2 of the '980 patent (SBR at 2).

The staff in its reply also argued that the claimed phrase "unaccompanied by . . . other extraneous protein bound thereto" should "not" be interpreted to refer to

It argued that where claim 2 refers to a product that is "unaccompanied by ... other extraneous protein bound thereto", it is referring to a human growth hormone expression product that has not been expressed in a conjugate form "as is clear from the pertinent discussion in the specification", and that only where the product is expressed in conjugate form is the product accompanied by extraneous protein bound to the desired product and thus be taken out of claim 2 of the '980 patent. It is argued that claim 2 is practiced when the desired product is not expressed as a conjugate, i.e. does not have extraneous protein covalently bound to the desired product as part of the polypeptide chain being expressed and that

that the fact that

is not relevant to whether claim 2 has been practiced; and that BTG has not cited any support in the '980 specification or '980 prosecution history for BTG's construction of claim 2 to

include

(SBR at 3, 4). The staff further argued that in view of the relative lack of support in the '980 specification or elsewhere for BTG's construction of "human growth hormone" and the "more logical contrary construction" set forth by the staff in its initial post hearing brief, claim 2 of the '980 patent is likely to encompass the production of a polypeptide that may or may not have the additional methionine attached to the amino acid chain. It also argued that the use by BTG of process steps that are in addition to the steps of said claim 2 does not avoid that claim (SBR at 5).

1. Claim Interpretation

Referring to claim 2 in issue of the '908 patent (FF 141), BTG has argued that the '980 patent describes a method of producing an inactive protein, not a biologically active human growth hormone; that human growth hormone is a protein composed of 191 amino acids and the inventors never made that protein; and that if the phrase "human growth hormone" in claim 2 is interpreted to mean both human growth hormone and met-human growth hormone, then claim 2 is indefinite (RB at 75, 76).

While BTG has argued that the '980 patent describes a method of producing an inactive protein, the language, at least, of the specification of the '980 patent is to the contrary. Thus the inventors of the '980 patent specifically disclose under the heading "Summary of the Invention" that "[m]icrobial sources for human growth hormone made available by the invention offer, for the first time, ample supplies of the hormone for treatment of hypopituitary dwarfism" (FF 154). Accordingly, based on specific language of the '980 specification, the administrative law judge finds that the first and fourth (last) occurrences, in claim 2 of the '980 patent (FF 141), of "human

growth hormone" is likely to be interpreted as a biologically active material suitable for the treatment, for example, of hypopituitary dwarfism.

With respect to the second and third occurrences of "human growth hormone" in said claim 2, viz. in the phrase "express a gene for human growth hormone unaccompanied by the leader sequence of human growth hormone or other extraneous protein bound thereto" (FF 141) (Emphasis added), the administrative law judge considers it important that one recognize what one skilled in the art (FF 86) would have known as of the July 5, 1979 initial filing date of the '980 patent (FF 145) without knowledge of the disclosure of the '980 patent and with knowledge of the disclosure of the '980 patent. In the former situation, such a person would know that a reduced precursor molecule of human growth hormone in an oxidizing atmosphere readily yields the medically active human growth hormone (FF 167); that it was impossible to obtain human growth hormone consisting of 191 amino acids in the cells of a human pituitary or ever in a bacterial cell because of the reducing atmosphere (FF 104, 119-121); that there were real difficulties using the synthetic gene approach of the '619 patent to produce human growth hormone (FF 73, 75); and that microbial polypeptide expression for production of human growth hormone was impossible because expression products produced contained leader sequences which prevented the production of medically active human growth hormone, in contrast to eukaryotic (human) cells where leader sequences were enzymatically removed as the material leaves certain cells in the pituitary glands, and because the entire amino acid sequence needed for human growth hormone was not able to be obtained (FF 63, 75, 119).

A person skilled in the art on July 5, 1979, and having the knowledge of the '980 patent, however, would learn that the named inventors of the '980

patent have provided methods and means for expressing quasi-synthetic genes wherein reverse transcription provided a substantial portion, preferably a majority of the coding sequence for human growth hormone, viz. codons for amino acids 24-191 (FF 154); that synthesis of the remainder of the coding amino acid sequence for the human growth hormone afforded a completed gene capable of expressing a polypeptide unaccompanied by the bio-inactivating leader sequences or other extraneous protein (FF 154); that the microbial polypeptide expression product of the '980 patent avoids both intracellular proteolysis and the necessity of compartmentalizing the bioactive form in extraneous protein pending extracellular cleavage (FF 154); that as shown by the '980 patent's section titled "Detailed Description of the Invention", the invention's general approach involved the combination in a single cloning vehicle of plural gene fragments which, in combination, code for expression not of human growth hormone as it is secreted from the pituitary glands but of a product containing a substantial portion of the codons for human growth hormone, with or without a terminal met,[10] (FF 155) which product contains the amino acid sequence essential for the identity and the chemical characteristics of human growth hormone (FF 122, 123, 126) and that after culturing and expression and in the presence of an oxidizing atmosphere there is obtained human growth hormone with or without a terminal met which can be easily detected by direct radioimmunoassay (FF 148) and which is obtainable in quantities and for applications unattainable before the '980 patent (FF 154). A person of ordinary skill in the art would also learn from the disclosure of

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[10] All mammalian proteins expressed in bacteria will begin with a met. Processing will always be necessary, to one degree or another, after expression in a bacterial cell to get the expressed product in action, usable form (FF 139).

the '980 patent that the obtained human growth hormone may or may not have the methionine at the amino-terminal end (FF 101, 157).

Based on the foregoing the administrative law judge finds that one skilled in the art would interpret the second and third occurrences of "human growth hormone" in claim 2 as referring to the expression of a gene for human growth hormone which gene has been transcribed and translated into an amino acid sequence critical for defining the identity and chemical characteristics of human growth hormone, lacks the leader sequence and may or may not contain a methionine. Moreover the administrative law judge, based on the foregoing, interprets the claimed phrase "unaccompanied by the leader sequence . . . or other extraneous protein bound thereto" as an expressed material unaccompanied by conjugate protein and bio-inactive conjugates, the necessity of the expression of which requires diversion of resources within the organism better committed to construction of the intended product (FF 73, 154). Finally the administrative law judge finds that claim 2 does not require that expression of the desired material must take place during the culturing step in view of the disclosure in the specification involving identification of the human growth hormone after the culturing step (FF 148) and especially because claim 2 states only that there must be culturing of cells having plasmids that "will" express a gene for human growth hormone (FF 141).

Moreover, any use by the inventors in the '980 patent of the term "human growth hormone" to refer broadly to all forms of human growth hormone, i.e. when it is inactive immediately after expression from the microbial cell with or without a methionine at the amino terminal end or when it becomes folded and active outside the cell upon purification with or without a methionine at the amino-terminal end is consistent with the usage in other patents,

by complainant in its annual report, by BTG in materials sent by BTG's president Fass to the United States Congress and in BTG's glossary (FF 93-100, 106-107, 139).

2. Validity of Claim 2 of the '980 Patent Under 35 U.S.C. § 103

BTG argued that the claimed invention of claim 2 of the '980 patent was obvious at the time it was allegedly made to those of ordinary skill in the art over complainant's '619 patent alone or in view of a Goodman et. al publication in "Specific Eukaryotic Genes (eds Engberg et. al) pages 179-190 (Munskagaard, Copenhagen, 1979) and Goodman at al U. S. Patent No. 4,363,877. It was argued that since complainant contends that the '619 patent discloses direct expression of human growth hormone, which complainant must argue in order to establish its case of alleged infringement, the '619 patent discloses the essence of claim 2 of the '980 patent; and that, to the extent that the '980 patent claim 2 also required expressing a gene for human growth hormone, that gene is disclosed in the Goodman et al references. Thus it is argued that a person of ordinary skill in the art would have found the invention of claim 2 of the '980 patent obvious in July 1979, when the patent application for the '980 and '832 patent was first filed (RB at 77, 78).

Earlier in this initial determination the administrative law judge found that there is a reasonable likelihood that complainant will not be able to show that the '619 patent discloses the expression of human growth hormone. Accordingly, the administrative law judge finds that there is not a reasonable likelihood that BTG will establish that claim 2 of the '980 patent is obvious.

3. Validity of the '980 Patent Under 35 U.S.C. § 112

BTG argued that the '980 patent is invalid under 35 U.S.C. § 112 because BTG has showed that the '980 patent describes a method of producing an

inactive protein, not a biologically active human growth hormone; that claim 2 is indefinite if it means both "human growth hormone and met-human growth hormone" and because of the use of the term "bound"; and that the inventors named in the '980 patent failed to disclose enablement of the claim 2 process in their application for the '980 patent when it was initially filed on July 5, 1979 although the inventors were well aware of details relating to the production of human growth hormone as of the time the initial application was filed (RB at 75, 76).

The administrative law judge rejects BTG's argument that the '980 patent is invalid under 35 U.S.C. § 112 because the '980 patent describes a method of producing an inactive protein and/or because claim 2 is indefinite. See Section VII B 1, supra.

With respect to BTG's enablement argument, BTG argued that the inventors assumed that human growth hormone was recovered from a supernatant or extract, whereas in fact, met-human growth hormone was precipitated in inclusion (refractile) bodies; and that standard purification methods are not applicable to human growth hormone in inclusion bodies (RB at 76,77). The inventors however in the '980 patent did disclose a purification process (FF 158). Moreover based on testimony of experts in this investigation, and other scientists, including scientists from BTG (FF 158 to 160, 162 to 166), BTG's argument on enablement is rejected. Accordingly the administrative law judge finds that there is not a reasonable likelihood that BTG will establish that the '908 patent is not valid under 35 U.S.C. § 112.

4. Alleged Infringement of Claim 2

BTG's accused process is set forth in the findings. See FF 90, 92, 110-114, 116-118. Based on those findings and the administrative law judge's

interpretation of the language of claim 2 See VII C 1, supra, the administrative law judge finds that the BTG process in issue and comprising

Accordingly the administrative law judge finds that there is a likelihood that complainant will establish that BTG literally infringes claim 2 of the '980 patent.

D. The '832 Patent

Complainant argued that BTG's expert

that claim 1 of the '832 patent deals with the production of the "first gene fragment" of the invention - - the cDNA fragment - - in two subparagraphs, numbered (a) and (b); that said subparagraph (a) states that the first fragment "comprises at least a portion of the coding sequence for said polypeptide" and as the '832 specification states, that cDNA fragment may, initially, be either larger or smaller than the desired polypeptide coding sequence; that said subparagraph

(b) of claim 1 of the '832 patent then deals with the circumstance in which the cDNA is initially larger in that it states that "where the first fragment comprises . . . codons for amino acid sequences other than those contained in said polypeptide," those unwanted codons are to be "eliminat[ed]", which applies to eliminating leader sequence codes; and that after paragraph (b), claim 1 describes the ultimate content of the cDNA fragment, stating that "the product of step (a) or, where required [i.e., if there is a leader sequence to start], step (b), being a fragment encoding less than all of the amino acid sequence of said polypeptide" and that whether the cDNA starts out longer than, or shorter than the codon sequence for the polypeptide of interest, it ends up shorter, being cut per paragraph (b) if necessary to make it shorter (CB at 33-36).

Complainant argued that BTG

Thus complainant argued that claim 1 calls for "obtaining [the first fragment] by reverse transcription from messenger RNA"; that reverse transcription is the process for making cDNA; that the claimed phrase "obtaining by reverse transcription" is the inventors' way of stating that the first fragment is cDNA and when scientists refer to cDNA, they do not limit the term to the original molecule directly obtained by the use of reverse transcriptase, but use the term to apply to clones of that original molecule as well since otherwise cDNA, as a term, would have little

use because when scientists make cDNA they always clone it to provide enough copies for use in the plasmids they are trying to construct; that BTG's expert

Complainant also argued that the claimed word "obtaining" is broad enough to cover a multi-step procedure in which a long cDNA is obtained by reverse transcription, which long cDNA is cloned and the clone is then cut to produce the "first fragment"; that the word "directly" does not appear in, and should not be read into, claim 1 of the '832 patent after the word "obtaining"; that scientifically

is

defining the word "gene" in a way contrary to the specification of the '832 patent because the codons for the 191 amino acids of hGH are referred to in the '832 specification as the "structural gene" with the full "gene" including not only the "structural gene," but the control region and the leader sequence

codons, if present; and that the '832 specification clearly distinguishes between the "structural gene" and the "gene" (CB 37-38).

Complainant argued that, with the proper interpretation of claim 1, of the '832 patent, it is clear that BTG

It is argued that the only other '832 infringement issue is whether BTG's

that the promoter is part of the "control region," and directs the transcription portion of the expression process; that while BTG

Complainant accordingly argued that there is no difference whatsoever between the sort of "control" that BTG's promoter exercises and what is described in the '832 patent (CB 38-39).

BTG argued that it does not infringe claim 1 of the '832 patent; that BTG did not construct "a replicable cloning vehicle capable, in a microbial organism, of expressing a particular polypeptide of known amino acid sequence"; that to the contrary BTG constructed

The staff argued that BTG practices all of the elements of claim 1 of the '832 patent and thus infringes that claim. It is argued that the BTG

Thus the staff argued that it is probable that it will be determined that BTG's process for constructing a plasmid involves the claim 1 step of "obtaining by reverse transcription from messenger RNA a first gene fragment . . . which gene fragment comprises at least a portion of the coding sequences" for human growth hormone (SB at 39-40).

The staff argued that

Thus the staff argued that it is likely that BTG's process for constructing a plasmid will be shown to involve the claim 1 step of "providing by organic synthesis one or more synthetic non-reverse transcript-gene fragment encoding the remainder of the amino acid sequence" of human growth

hormone (SB at 40).

The staff also argued that the BTG process involves

The staff argued accordingly that the BTG process satisfies the claim element of deploying the synthetic gene fragments and the reverse-transcript fragments in a replicable cloning vehicle in proper reading phase relative to one another and further that the deployed gene fragments are deployed in relation to an expression promoter so that the expression promoter will cause transcription, resulting in the expression of human growth hormone (SB at 41).

Complainant, in reply, argued that a particularly egregious example of BTG's effort at misdirection is its continual focus on

one act of infringement, at any time after a patent issues is enough to create liability; and that Gottesman admitted at the hearing that construction of the plasmids was essential to the production of human growth hormone (CBR at 11).

The staff, in reply, argued that while BTG maintains that it

it is not clear what distinction BTG is trying to make with respect to claim 1 of the '832 patent, especially since BTG does not contest the fact that its

replicable cloning vehicle expresses a polypeptide of "known amino acid sequence" as required by claim 1 of the '832 patent (SBR at 6).

The staff further argued, in its reply, that claim 1 of the '832 patent calls for a step of obtaining a first gene fragment "by reverse transcription from messenger RNA"; that BTG argues that

the problem that the '832 invention addressed, viz. that the reverse transcription of messenger RNA is likely to result in a gene that is either too short or too long, i.e. is likely to yield DNA coding for less than all of the 191 amino acids of human growth hormone or DNA coding for 191 amino acids of human growth hormone or DNA coding for 191 amino acids plus the leader sequence; that

In the staff's view the fact that BTG

does not take the BTG process out of step (a) of claim 1. Hence the staff argued that it is likely to be found that this portion of the BTG process satisfies the step (a) claim language "obtaining by reverse transcription from messenger RNA a first gene fragment" (SBR at 7).

In reply the staff argued also that even if step (a) of claim 1 of the '832 patent is held not to cover the BTG process for obtaining its first gene fragment, it will be found that the process

is covered in step (b) of claim 1 of the '832 patent; that with regard to the situation "where the first fragment comprises protein-encoding codons for amino acid sequences other than those contained in said polypeptide", i.e. where the cDNA is larger than that needed to express the desired polypeptide, claim 1 calls for eliminating the excess "while retaining at least a substantial portion" of the coding sequence for the desired polypeptide, viz. the codons for the leader sequence must be cut away but in such a manner as to retain at least a substantial portion of the coding sequence for the desired polypeptide, col. 5, lines 40-45, col. 6, lines 47-48 of the '832 patent stating "[c]leavage will delete DNA for the unwanted leader" and the '832 specification providing that microbial cells cannot be relied upon to remove the leader sequence from the expression product

> "and it is accordingly desirable to remove sequence coding for such signals or leader sequences from the

mRNA transcript. In the course of that removal process the translation start signal is also lost, and almost invariably some codons for the intended product will be removed as well" (CX 3, '832 patent, col. 5, lines 40-45);

and that BTG

The staff in its reply further

The staff argued that

It is argued that the fact that BTG used additional steps to construct the plasmid does not avoid claim 1 of the '832 patent (SBR at 10-11).

In the staff's reply it was additionally argued that while BTG contends that its process does not meet the requirement of claim 1 of the '832 patent, viz. that the expression plasmid be placed "under the control of an expression promoter",

BTG, in its reply, argued that to prove infringement, complainant must show that every step of process claim 1 of the '832 patent or its equivalent has been practiced by BTG and that complainant concedes that BTG has not practiced step (a) of claim 1 of the '832 patent; that said step (a) requires obtaining a first gene fragment from mRNA by reverse transcription and as complainant admits "BTG got cDNA from Goodman"; and that as BTG simply "got" the cDNA from a prior art source, then it did not practice step (a) of the process of claim 1 of the '832 patent and does not infringe that claim, citing Julien v. Zeringue, 864 F.2d 1569, 1571 (Fed. Cir. 1989) cert. denied 493 U. S. 917 (1989) (Julien) (RBR at 38-39).

BTG also argued in its reply that the full length cDNA corresponding to the entire gene plus the leader sequence, which BTG received from the Goodman group at the University of California "with no strings attached," was not a gene fragment. BTG argued that there can be little doubt that BTG's plasmids, however prepared, are not products imported by BTG into the United States and that complainant does not so claim, that complainant concedes that claim 1 of the '832 patent is "in form a method of making the cloning vehicle"; that it cannot be asserted that human growth hormone, or the protein anti-human growth hormone (-13 hGH) are plasmids or cloning vehicles; that BTG performs numerous steps to

and

that the essential character and utility of the final product have nothing whatsoever to do with the essential character and utility of the plasmid cloning vehicle (RBR at 38, 39).

Complainant's counsel, in closing argument, argued that when he read some of BTG's proposed "rebuttal stuff" on the '832 patent, he was "flabbergasted"; that there is not any dispute that when BTG got the first fragment in issue in claim 1 of the '832 patent, instead of BTG actually making it themselves, BTG took a donation of it from the University of California people and so the actual step of getting the mRNA and carrying out the reverse transcription was performed by the University of California people; that the law does not support the notion that one can avoid infringement of a claim by calling up somebody and asking that somebody to perform a first step of a claim and then give to the alleged infringer the product of that first step; and that BTG's argument is a "new argument that came out for the first time in . . .[BTG's] rebuttal papers" (Tr. at 2764-2765). When the administrative law judge, at closing argument asked whether anybody had addressed this "legal point" in their briefs, complainant's counsel said that complainant had not "because I didn't realize until late last night that they [BTG] were making this argument. I have not - - if it's in their earlier papers, it certainly went by me." (Tr. at 2772-2773). Complainant's counsel did represent that he had a chance to read Julien and the case has nothing to do with the issue "in front of us"; that in Julien there was a product claim in which there was a combination of mechanical elements and the Court found that in the alleged infringement some of the elements were missing altogether; and Julien was not a case in which the

elements were all there in a method claim but one of the steps had been carried out by somebody else and then the fruit of it was transferred to the alleged infringer (Tr. at 2811, 2812).

BTG's counsel, at closing argument, replied that step (a) of claim 1 of the '832 patent was performed before BTG even existed as a company and it was not performed under some kind of a subcontract and hence the University of California's Goodman was not BTG's agent. BTG's counsel agreed that BTG obtained a "full length" cDNA from the University of California but argued that in that sense BTG did not obtain by reverse transcription anything. It was further argued that what BTG obtained was not a gene fragment, as that term is used in step (a) of claim 1 of the '832 patent,

It was also argued that if in fact, subsequent to the issuance of a patent, two parties entered into some contract whereby they divided up the work of doing a patented process, then BTG's counsel would think there would result a legally different conclusion than in the situation where the step (a) of claim 1 of the '832 patent was performed by the University of California's Goodman "prior to the filing the patent application by Genentech which is in suit"; that this is not just an issue that somebody else did something at some point in time as an accommodation to BTG; and that what is involved is that the prior art did step (a) of claim 1 of the '832 patent and it was done before complainant even filed a patent application (Tr. at 2773-2774).

The staff at closing argument argued that an issue has been framed in terms of subcontractors; that the record is that BTG did not do any reverse transcription with respect to step (a) of claim 1 of the '832 patent; and that "we've got ourselves an issue of law here" (Tr. at 2769). The staff later,

while admitting that it did not cite anything in its brief on the subcontractor issue, made reference to Ralston Purina Co. v. Far-Mar-Co., Inc. 586 F. Supp. 1176 (D. Kan. 1984) (Ralston Purina), Metal Film Company v. Metlon Corporation, 316 F. Supp. 96 (S.D.N.Y. 1970) (Metal Film), and Chisum, Patents 16.02[6], and argued that it does not appear that there is any support for BTG's argument that one can import a product that has been made by a patented process but can avoid a violation of section 337 by merely noting that it was more than one person engaged in the process for making the imported product (Tr. at 2858-60).

1. Claim Interpretation

Claim 1 of the '832 patent concerns the improvement of a method of constructing a replicable cloning vehicle capable, in a microbial organism, of expressing a particular polypeptide of known amino acid sequence involving inserting a gene coding for the polypeptide placed under the control of an expression promoter into a cloning vehicle (FF 168).[11] There is no step of expression in said claim. Rather a replicable cloning vehicle capable of expressing a particular polypeptide of known amino acid sequence is obtained (FF 177).

The improvement, according to claim 1 of the '832 patent, comprises steps (a), (b), (c) and (d) (FF 168). In the practice of claim 1, step (a) is always required. Thus it cannot be omitted. Step (b) may or may not be utilized in the practice of claim 1 (FF 171). The specification of the '832 patent makes such clear when it states that the invention admits of manifold

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[11] The '832 patent issued on August 3, 1982 on Ser. No. 55,126 filed July 5, 1979 (FF 169, 170). The specifications of the '980 and '832 patents are identical in all substantive aspects (FF 170).

applications, each having in common certain attributes, including employing an a mRNA transcript which codes for a substantial portion of the intended polypeptide's amino acid sequence but which, if expressed alone, would produce a different polypeptide either smaller or larger than the intended product (FF 157). Thus the administrative law judge agrees with complainant (CB at 35) that in interpreting claim 1 of the '832 patent, claim 1 not only deals with the leader sequence problem, i.e., where the cDNA has extra codons over and above those that code for the polypeptide of interest but also with the opposite situation, in which the cDNA from the outset is missing some of the codons needed for the particular polypeptide.

Steps (c) and (d) of claim 1 of the '832 patent are always utilized in the practice of claim 1 (FF 171).

Step (a) obtains by reverse transcription from messenger RNA a first gene fragment for an expression product other than said polypeptide which fragment comprises at least a portion of the coding sequence for said polypeptide (FF 168). According to the specification, obtaining "a first gene fragment" involves the use of reverse transcription by means of standard methods (FF 180).[12] The specification also teaches that the claimed recitation "fragment comprises at least a portion of the coding sequence for said polypeptide" means preferably at least a majority of the codons for the desired product (FF 180) and moreover, as stated in the specification (FF 190), the first fragment (cDNA fragment) may initially be either larger or smaller than the desired polypeptide coding sequence.

Step (b) of claim 1 has the phrase "where the first fragment comprises .

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[12] The term "complementary or 'cDNA'" has been used to refer to reverse transcription of DNA (FF 28, 75).

. . codons for amino acid sequences other than those contained in said polypeptide, eliminating the same while retaining at least a substantial portion of said coding sequence" (FF 168). The administrative law judge finds that such language, in view of the '832 specification, deals with the circumstance in which the starting cDNA first fragment contained by reverse transcription from messenger RNA, is initially larger and hence paragraph (b) may apply to eliminating leader sequence codons.

Claim 1 of the '832 patent has the phrase "the product of step (a) or, where required, step (b) being a fragment encoding less than all of the amino acids sequence of said polypeptide" (FF 168) which phrase separates the step (b) and the step (c) recitations. The specification teaches that the claimed recitation "less than all of the amino acid sequence" means preferably at least a majority of the codons for the desired product (FF 180). The administrative interprets this phrase as meaning whether the cDNA starts out longer than, or shorter than the codon sequence for the polypeptide of interest, it ends up shorter, being cut per paragraph (b) if necessary to make it shorter.

Step (c) of claim 1 has the phrase "providing by organic synthesis one or more synthetic non-reverse transcript-gene fragments encoding the remainder of the amino acid sequence of said polypeptide, at least one of said fragments coding for the amino-terminal portion of the polypeptide" (FF 168). The '832 specification indicates that this step will involve the insertion of a codon at the end of the gene to provide a site for initiation of translation and that will encode for a methionine amino acid (FF 175).

Step (d) of claim 1 of the '832 patent requires "deploying the synthetic gene fragment(s) of step (c) and that produced in step (a) or (b), as the case

may be, in a replicable cloning vehicle in proper reading phase relative to one another" (FF 168). This claim element requires deployment of the reverse transcription gene fragment and deployment of the synthetic gene fragments in a replicable cloning vehicle in proper alignment with one another so as to allow for expression of the entire constructed gene (FF 181).

The last phrase of step (d) of claim 1 reads "and under the control of an expression promoter (FF 168). This last phrase refers to the use of an expression promoter that is the source of expression," capable of "causing" the initiation of transcription of the gene in the cell (FF 182).

2. Validity of Claim 1 under 35 U.S.C. §§ 101 and 103

BTG argued that the '832 patent is invalid under 35 U.S.C. § 101 and 103. It is argued that in fact, the human growth hormone cDNA fragment encoding amino acids 24-191 of human growth hormone was obtained from the Goodman group at the University of California; that since claim 1 is in Jepson format, the prior art and the alleged novel step of the improved process must be clearly differentiated; and that by using the Jepson format, complainant is deemed to rely for novelty on the subject matter "following the improvement which comprises transition phrase" which in this case one step clearly was in the prior art and was not novel (RB at 81).

It was also argued by BTG that the claimed invention of the '832 patent, as a whole, was obvious at the time it was allegedly made to those of ordinary skill in the art over Goodman et. al U.S. Patent No. 4,363,877 (RBX-119), alone or the Goodman et. al publication in "Specific Eukaryotic Genes (eds Engberg et. al) pages 179-190 (Munskagaard, Copenhagen, 1979) (RBX-120) in view of Bahl et. al "Biotechnical and Biophysical Research Communications" Vol. 81, No. 3 (April 14, 1978) pages 695-703 (RBX-121). BTG argued that the

Goodman references show prior art work in obtaining by reverse transcription cDNA encoding amino acids 24-191 of human growth hormone; that Goodman et al discloses the first step of claim 1 of the '832 patent; and that Bahl uses organic synthesis to produce oligonucleotides for attachment to the end of DNA encoding a polypeptide and to obtain a plasmid which expresses the polypeptide (RB at 81, 82).

At the outset, BTG cites no authority for the proposition that since claim 1 of the '832 patent is in "Jepson" format, the prior art and the alleged novel step of the improved process must be clearly differentiated. Sjolund v. Musland, 847 F.2d 1573, 1577 (Fed. Cir. 1988) states that a preamble of a Jepson claim is only "impliedly admitted to be prior art" citing Pentec, Inc. v. Graphioc Controls Corp., 776 F.2d 309, 315 (Fed. Cir. 1985) (Pentec) and added the condition that "the specification confirms this implied admission." Id. In Pentec the Court qualified any implied admission with the phrase "unless the preamble is the inventor's own work." In addition, referring to the Manual of Patent Examining Procedure (MPEP) 608.01(m) (5th ed. 1983), the Court stated that even with a Jepson claim the claimed invention consists of the preamble in combination with the improvement. Id.[13]

The administrative law judge rejects the BTG's argument that one step of claim 1 of the '832 patent "clearly was in the prior art" (see Section VII E

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[13] Section 608.01(m) of the MPEP, with a revision date of May 8, 1988, states in pertinent part:

> The form of claim required in 37 CFR 1.75(e) is particularly adapted for the description of improvement type inventions. It is to be considered a combination claim. The preamble of this form of claim is considered to positively and clearly include all the elements or steps relied therein as a part of the claimed combination.

infra relating to enforceability of the '832 patent). Moreover, assuming one step of claim 1 was in the prior art, he finds nothing in the prior art to suggest the claimed combination.[14] See ACS Hospital Systems, Inc. v. Montefiore Hospital, 732 F.2d 1572, 1577 n. 14 (Fed. Cir 1984); Lindemann Maschinenfabril GmbH v. American Hoist and Derrick Co., 730 F.2d 1452, 1462 (Fed. Cir. 1984). Accordingly the administrative law judge finds that BTG has not shown a reasonable likelihood of success in establishing that claim 1 of the '832 patent is invalid under 35 U.S.C. 101 and/or 103.

3. Alleged Infringement of Claim 1

At the outset complainant has admitted that the actual step of getting messenger RNA and carrying out the reverse transcription called for by step (a) of claim 1 was performed by Goodman at the University of California (FF 172). BTG has argued that it does not infringe claim 1 because it does not perform step (a). Step (a) is essential in the practice of claim 1 of the '832 patent (FF 171).

In Julien, cited by BTG, the Federal Circuit affirmed the judgment of the district court that certain claims were not infringed, finding that when a

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[14] With respect to the claimed combination steps of claim 1 of the '832 patent, the claimed method calls for creating a particular DNA sequence by first preparing cDNA from mRNA which was highly enriched for hGH mRNA. The mixture of cDNA was treated with a protein called a "restriction endonuclease," an enzyme which cuts DNA at a specific sequence. This allowed the inventors Goeddel and Heyneker to remove the leader sequence and to clone a fragment of the hGH gene which lacked the leader sequence. That fragment also lacked a portion of the human growth hormone gene. The portion missing was the beginning of the gene -- the amino-terminus. The next step was to chemically synthesize a piece of DNA coding for the missing portion of the gene. That was possible because the length of the sequence missing was not prohibitively long. Those two fragments, the cDNA and the chemically synthesized sequences, were then combined to produce a semi-synthetic gene encoding the desired protein which in turn can be used to produce hGH (FF 188).

claim limitation, both literally and equivalently, is missing, there can be no infringement. Julien, 864 F.2d at 1571. In the factual situation in issue there is no claim limitation missing. In Ralston Purina, cited by the staff, the Court stated that it is well settled that a party cannot avoid infringement merely by having a third party practice one or more of the required steps. Ralston Purina 586 F. Supp. at 1219. In Metal Film, also cited by the staff, the Court found that there was infringement and noted that although the infringers chose outside suppliers to do the "vacuum metallizing," which step was called for by the claim in issue and which was said to be a conventional step, such choice did not mitigate the infringement of the overall process. Metal Film, 316 F. Supp. at 99. It would appear in the factual situation before the administrative law judge that BTG did not contract to have any portion of step (a) of claim 1 of the '832 patent done for it. The section of Chisum which the staff referred to does cite Mobil Oil Corp. v. Filtrol Corp. 501 F.2d 282 (9th Cir. 1974) and makes reference to the statement of the Ninth Circuit that "[w]e question whether a method claim can be infringed when two separate entities perform different operations and neither has control of the other's activities."

The administrative law judge finds that at least the complainant has not developed the legal issue with respect to whether claim 1 of the '832 patent is infringed by BTG when apparently it was performed before BTG even existed as a company and step (a) was not performed under any kind of a subcontract between the University of California and BTG.[15] Accordingly, because

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[15] On this point, in Certain Integrated Circuit Telecommunication Chips and Products Containing Same, Including Dialing Apparatus (Telecommunication Chips) this administrative law judge found a lack of utility in certain of one of the patents in issue, and followed a claim interpretation urged by the (continued...)

complainant has the burden of showing that there is a reasonable likelihood that it will establish that claim 1 is infringed and because complainant has not established that the role of Goodman with respect to step (a) of claim 1 was irrelevant in finding that said claim 1 is infringed by BTG, the administrative finds at the present time that complainant has not met said burden.

Assuming complainant has established that BTG would infringe claim 1 even though BTG did not practice step (a) of claim 1 of the '832 patent, the administrative law judge would then find that there is a reasonable likelihood that complainant will establish that BTG infringes claim 1 with respect to any other issues raised by BTG.

Referring to the preamble of claim 1 the administrative law judge finds that BTG

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[15](...continued)
respondents and the staff Telecommunication Chips. ID (March 9, 1993) at 30-31. On review, the Commission agreed with and adopted the construction of the claims set forth in the initial determination, but with respect to the finding regarding utility, stated that '[p]rior to the issuance of the ID, neither complainant nor respondents . . . had presented arguments concerning whether the asserted claims would have utility under . . . [complainant's] claim construction," and concluded that "[i]n view of the lack of development of the utility issue, and because we view the ALJ's contingent finding analysis unnecessary to proper claim construction, we vacate the contingent finding and the supporting analysis." Telecommunication Chips, Commission Opinion On The Issues Under Review and On Remedy, The Public Interest And Bonding (June 9, 1993) at 13.

The administrative law judge finds further that BTG practices step (c) and (d) in the subsequent steps of its process (FF 181, 192). Finally, the administrative law judges finds that BTG practices step (d) in that

BTG's position is that

Both

positions are rejected.

There is no general agreement as to the exact usage of the term "gene",

since several criteria that have been used for its definition have been shown not to be equivalent (FF 18). Moreover, the '832 patent draws a clear distinction between a structural gene which is that portion that can encode the 191 amino acids and the word "gene" which can be given a broad meaning (FF 18, 189). Moreover, the administrative law judge finds that a man skilled in the art would consider as still being an "mRNA transcript fragment" (FF 193(a)).

As to what BTG

is found to be completely consistent with the alternatives set out in the '832 specification and in claim 1 (FF 193(a)).

Based on the foregoing the administrative law judge would find, assuming complainant can established that BTG infringes claim 1 of the '832 patent even though BTG does not perform step (a) of claim 1, that it is likely that complainant will be able to establish that BTG literally infringes claim 1 of the '832 patent. Thus as encompassed by claim 1 of the '832 patent BTG, in its accused process,

On this

point, when BTG's Gottesman was asked whether BTG did "exactly what column 5 of the '832 patent told the world was desirable,"

E. Enforceability of the '980 and '832 Patents

BTG argued that the named inventors of the '832 and '980 patents failed to disclose the prior work done by the Goodman group, leading to the cDNA used to produce human growth hormone and that the inventors' failure to disclose this material information to the United States Patent Office (PTO) is inequitable conduct which renders said patents unenforceable. It is argued that the inventors of the two patents in issue were well aware of the Goodman work at the time the initial application for the patents was filed on July 5, 1979; that there was even a scientist in common, Dr. Peter Seeburg and Dr. Axe Ullrich and a dispute arose whether Drs. Seeburg and Ullrich took the cDNA from the University of California to complainant; and that BTG showed that complainant's intentional failure to disclose the true source of its cDNA gene fragment, as revealed in the named inventors' article in Nature (1979) makes the '832 and '980 patents unenforceable (RB at 83, 84).

Complainant argued that BTG's assertion is based on rank speculation and is contrary to the laboratory notebook evidence that complainant made its own human growth hormone cDNA; that it was also no secret, even to the PTO, that the Goodman group had human growth hormone and also no secret that the group had "very few good ideas" about how to get rid of the leader sequence and hence that any cDNA obtained from Goodman only presented the problem of getting ride of the leader sequence and did not solve t hat problem (CB at 26,

27).

The staff argued that at the hearing on temporary relief, the evidence indicated that one of the inventors of the '980 and '832 patents synthesized cDNA gene fragments using RNA obtained from the University of California and thus the factual premise of BTG's unenforceability argument, i.e. that the cDNA fragments themselves were obtained from the University of California, is not supported by the record (SB at 36).

BTG has the burden of showing that there is a reasonable likelihood of success in BTG establishing that the '832 and '980 patent are unenforceable. Contrary to the allegations of BTG, there is laboratory notebook evidence that complainant made its own cDNA (FF 216, 217). While BTG argued that the notebook evidence cannot be substantiated at the hearing, citing Kleid, Tr. at 931, (BTG's rebuttal to complainant's proposed finding 263), the Tr. at 930 to 932 is not found to establish an alteration of the notebook evidence (FF 217). Accordingly, the administrative law judge finds that BTG has not shown that there is a reasonable likelihood that BTG will establish that the '832 and '980 patents are unenforceable.

F. The 35 U.S.C. § 271(e)(1) and Research Use Defenses

BTG argued that Genentech has failed to establish a likelihood of success on the merits because BTG's domestic activity falls within the "safe harbor" of 35 U.S.C. § 271(e)(1)[16] and the experimental use exemption. Thus

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[16] 35 U.S.C. § 271(e)(1) reads in full as follows:

> It shall not be an act of infringement to make, use, or sell a patented invention (other than a new animal drug or veterinary biological product (as those terms are used in the Federal Food, Drug, and Cosmetic Act of March 4, 1913) which is primarily manufactured using recombinant DNA, recombinant RNA, hybridoma

(continued...)

it argued that importation of -13 human growth hormone and human growth hormone for use in the research experiments were not infringing acts under the patent law because of the experimental use exemption and that importations of human growth hormone for use in the clinical trials are not infringing acts under section 271(e)(1) (RB 48-52). BTG further argued that there is no evidence of a single sale or offer for sale so there is no "constructive presence" as complainant alleged; that the only evidence of importation comprises some small shipments made without charge to that while complainant argued that use constitutes an act of infringement of at least one of the claims in the patents-in-issue, since all of the asserted claims are for processes for making plasmids, functional mammalian polypeptides or "human growth hormone", there was no infringement because no one claims that made any plasmid, polypeptide or human growth hormone (RBR at 46-47). It is argued that while both complainant and the staff characterized experiments as involving a commercial purpose, his experiments could not have been further removed from such a purpose; that all was given was some authentic human growth hormone for

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[16](...continued)

> technology, or other processes involving site specific genetic manipulation techniques) solely for uses reasonably related to the development and submission of information under a Federal law which regulated the manufacture, use, or sale of drugs or veterinary biological products. [Emphasis added]

The portion of section 271(e)(1) relating to recombinant DNA techniques was added to section 271(e)(1) by the 1988 Animal Drug and Patent Term Restoration Act, Pub. L. 100-670, 201(i)(1). The specific exception for recombinant DNA techniques contained in the parenthesis relates only to animal drugs and veterinary products, not to the human drugs accused in the complaint. Therefore, the exemption in 271(e)(1) applies to the types of products at issue here.

use as a control and several mutants, only one of which (-13 hGH) has been alleged to have been made by an infringing process; that there is no evidence of what did with the -13 hGH; and that -13 hGH's anti-growth hormone activity belies the argument that it is or is being used to develop a second-generation human growth hormone product (RBR at 47-48).

Complainant argued that BTG distributed of its hGH product to at the who performed studies using the hGH on rats and mice; that the uses of BTG's hGH in this manner did not correspond to any pending IND's (Investigational New Drug Application) and NDA's (New Drug Application) that are related to BTG's applications to obtain FDA approval to market its hGH product in the United States, and therefore constitute infringing uses under section 271(a); that the research results were published in a 1992 article entitled

that the article describes use of "biosynthetic wild-type human growth hormone," which is BTG's recombinantly produced hGH product having the identical amino acid sequence as natural hGH; and that use constitutes an act of infringement of at least one of the claims of the patent-in-issue (CB at 61-63). It also argued that section 337 jurisdiction is broader than the entire patent statute because it vests the Commission with the authority to remedy unfair acts not subject to the patent statute and that in contrast section 271(e)(1) provides a narrow exemption from charges of patent infringement when the infringement is conducted "solely for uses reasonably related" to the submission of data to the FDA for premarket regulatory approval of drugs or devices (CB 63 to 66).

The staff argued that, while the clinical trials conducted by BTG in an effort to secure FDA approval of its products appear to be of the type that are necessary to the FDA approval process and thus are exempt (noninfringing) under 35 U.S.C. § 271(e)(1), the evidence indicates that BTG, a commercial drug company, imported hGH into the United States in connection with

study to further its commercial interests and accordingly BTG will not likely be able to establish the elements of the research use defense to infringement in this investigation (SB at 43 to 49). The staff in its reply argued that complainant appears to argue that because it is asserting process claims in this investigation and subsection (a)(1)(B)(ii) speaks in terms of articles made by a process covered by the claims of a patent rather than "infringement", technical infringement is not required under section 337 and therefore section 271(e)(1) is not applicable. The staff however believes that that interpretation by complainant of subsection (a)(1)(B)(ii) as not requiring patent infringement is contrary to the Commission's long-standing practice of applying U.S. patent law in patent-based section 337 investigations and that complainant has cited no convincing authority to support its view that the section 271(e)(1) exemption to patent infringement is not applicable to patent-based investigations under section 337 (SBR at 15-16).

The administrative law judge finds that it is likely that BTG will not be able to establish that its domestic activity falls under the "safe harbor" of 35 U.S.C. § 271(e)(1) and research use defense. See FF 218 to 236, particularly FF 230, 231, 232, 233, 234, 235 and 236.

D. The 35 U.S.C. § 271(g)(1) Defense

BTG argued that the human growth hormone it imported is not made by an

infringing process within the meaning of 35 U.S.C. § 271(g)(1) of the Patent Law; that that section provides that a product made outside the United States by a patented process will not be considered to be so made if the product made by the patented process "is materially changed by subsequent processes to obtain another product which is then imported";[17] and that

BTG also argued that BTG's product cannot be assumed to have been made by complainant's claimed process because there are commercially viable non-infringing processes for making human growth hormone and referred to a process used by Serono for making human growth hormone involving production in mammalian cells (RB at 55).

Complainant argued that the section 271(g) issue as to the '980 patent can be analyzed in two different ways, reflecting the fact that claim 2 of the '980 patent can be read on producing hGH with or without the met; that the

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[17] 35 U.S.C. § 271(g) reads in part:

> Whoever without authority imports into the United States or sells or uses within the United States a product which is made by a process patented in the United States shall be liable as an infringer, if the importation, sale, or use of the product occurs during the term of such process patent. . . . A product which is made by a patented process will, for purposes of this title, not be considered to be so made after --
>
> (1) it is materially changed by subsequent processes; or (2) it becomes a trivial and nonessential component of another product. (Emphasis added).

"isolating and purifying" step of claim 2 of the '980 patent can be applied at any stage of BTG's

Complainant argued that claim 1 of the '832 patent, though in the form a method of making the cloning vehicle, has as one of its requirements that the cloning vehicle include the gene for expressing the "particular polypeptide," which can be viewed as either hGH or met-hGH; that while BTG's witnesses have insisted that

such is a matter of semantics; and that however one defines "production" the construction of the cloning vehicle is not only an essential prerequisite for expression and purification of the hGH but has such expression and production as its only purpose (CB at 45-46).

Complainant also argued that BTG's reliance on the Serono process to avoid § 271(g) liability is misplaced because BTG has not demonstrated the commercial viability of Serono's process; that unlike complainant, Serono makes hGH in mammalian rather than bacterial cells; that Serono has not received FDA approval to market its products in the United States; and that BTG has not even attempted to make a showing that mammalian hGH production is commercially viable (CB at 50).

The staff argued that the evidence indicates that

thus the process of

claim 1 of the '832 patent was used in the manufacture of the imported product although additional process steps were also required, viz. the expression, recovery, isolation and purification steps of the '980 patent. It argued that significantly the relationship between process steps for the construction of a plasmid and the end-product that is expressed by that plasmid was specifically addressed by Congress in the legislative history of section 271(g) as follows:

> In the biotechnology field it is well known that naturally occurring organism contain within them particular genetic sequences composed of unique structural characteristics. The patented process may be for the process of preparing a DNA molecule comprising a specific genetic sequence. A foreign manufacturer uses the patented process to prepare the DNA molecule which is the product of the patented process. The foreign manufacturer inserts the DNA molecule into a plasmid or other vector and the plasmid or other vecot [sic, vector] containing the DNA molecule is, inturn [sic], inserted into a host organism; for example, a bacterium. The plasmid-containing host organism still containing the specific genetic sequence undergoes expression to produce the desired polypeptide. Even if a different organism was created by this biotech procedure, it would not have been possible or commercially viable to make the different organism and product expressed therefrom but for the patented process, the product will be considered to have been made by the patented process.

S. Rep. No. 100-83, 100th Cong. 1st Sess. 51 (1987) (Emphasis added); and that the applicability of the above section to the instant investigation is supported by the testimony of

Hence the staff concluded that BTG is unlikely to be able to show that its imported product is materially different from the product of the '832 process within the meaning of 35 U.S.C. § 271(g). (SB 49-51).

The staff, in reply argued that there is no evidence that there was any feasible way for BTG to obtain the met-free hGH product that it imported into the United States without first producing the met-hGH for which it used the patented processes of claim 2 of the '980 patent and claim 1 of the '832 patent and hence that it is likely that BTG's imported met-free hGH will be found not to have been materially altered from the product of the patented processes of the '980 and '832 patents in issue (SBR at 20).

The administrative law judge finds that BTG's imported met-free hGH will be found not to have been materially altered from the process of claim 2 of the '980 patent in light of his earlier finding in this initial determination that said claim 2 can be read on producing hGH with or without the met. Moreover, based on earlier findings in this initial determination, he finds that the expressed BTG material has the critical amino acid sequence for human growth hormone and the conversion of BTG's expressed material to what is imported would not involve a material change within the meaning of 35 U.S.C. § 271(g)(1). Also in view of the legislative history of 35 U.S.C. § 271(g)(1), outlined above, the administrative law judge finds that it is unlikely that BTG will be able to show that its imported product is materially different from the plasmid of claim 1 of the '832 patent. He further rejects BTG's argument involving Serono. See FF 295(a).

H. Domestic Industry

Regarding the "non-patent" aspects of the domestic industry, the administrative law judge finds that there is a reasonable likelihood that complainant will succeed in establishing that a domestic industry exist (FF 244 to 264).

A comparison of complainant's process (FF 265 to 270) with BTG's process

(FF 90, 92, 110-114, 116-118) shows a similarity with respect to material steps of the processes of claim 2 of the '980 patent and of claim 1 of the '832 patent. In view of that similarity, the analysis of infringement set forth supra by the administrative law judge with respect to said claims is applicable to the question of whether complainant practices said claims. The administrative law judge finds that it is reasonably likely that complainant will succeed in establishing that it practices each of said claims. See in particular FF 267, 269, 270.

VIII. Non Technical Issues

A complainant is entitled to a presumption of irreparable harm when it clearly shows the validity and infringement of the patent asserted. Pressure Transmitters, Commission Opinion on Temporary Relief at 33, aff'd sub nom., Rosemount, Inc. v. U.S.I.T.C., 910 F.2d 819, 822 (Fed. Cir. 1990) (affirming that presumption of irreparable harm is appropriate when there is "strong preliminary showing" of validity and infringement); Smith International, 718 F.2d at 1581 (holding that immediate irreparable harm is presumed where validity and infringement are "clearly established"); Chrysler Motors, 908 F.2d at 954 (presumption of irreparable harm requires minimum of "strong showing" of validity and infringement). Such a showing a showing of validity and infringement must be "'not merely a reasonable but a strong showing indeed.'" Pressure Transmitters, Commission Opinion on Temporary Relief at 7, quoting Roper, 757 F.2d at 1271.

In view of the administrative law judge's findings with respect to the '980 patent, supra, complainant is entitled to a rebuttable presumption of irreparable harm in the absence of relief. However, as set forth infra, that presumption has been effectively rebutted by BTG.

A. Relevant Time Period

BTG argued that the relevant time period for determining harm in this TEO proceeding is only from the date of any FDA approval through July 1, 1994 because complainant, by requiring the Novo respondents in their consent order agreement to refrain from entering the U.S. hGH market until July 1, had "demarcated the precise contours of its alleged 'irreparable harm' claim" (RB at 12, n.28). At oral argument BTG argued that because complainant expects an affirmative initial determination on permanent relief in this investigation prior to July, complainant does not care what Novo does after July 1, 1994 (Tr. at 2952-53).

Complainant argued that the relevant time period is from March 7, 1994 (the date it expects FDA approval of BTG's NDA) through October 1, 1994 (the approximate date on which permanent relief, if any, will issue) (CBR at 21). Complainant further argued that its agreement with the Novo respondents demonstrates their willingness to forego litigation in exchange for certain obligations, and is completely independent of any harm complainant will suffer as a result of any post-July market entry by BTG (CBR at 20-21). Complainant at oral argument argued that the consent order agreement approved by the administrative law judge[18] and the Commission settles the dispute with respect to fewer than all the respondents; that if an agreement that covers all of the relevant time involved cannot be worked out with all of the respondents then

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[18] Although the administrative law judge approved the consent order agreement between complainant and Novo (see Order No. 22 (Oct. 19, 1993)), the agreement was considered as part of a motion to terminate the temporary relief phase of this investigation as to one set of respondents. The administrative law judge did not then consider the relevant period for considering irreparable harm nor what evidentiary significance the agreement had with respect to the remaining set of respondents. Neither did any response to the motion to terminate focus an any such evidentiary significance.

there would be no settlement because the remaining respondents would use the agreement to imply a concession by complainant; and that the reason for the July 1 date is because complainant expects a favorable result with respect to the initial determination on permanent relief and expects to be able to use it as a basis to obtain a TRO in district court (Tr. at 2957-59).

The staff argued that the relevant period as a matter of law is "between now and the conclusion of the investigation" i.e. to September 29, 1994; and that the statute speaks in terms of irreparable harm in the absence of temporary relief which, if granted, runs to the end of the investigation. However, the staff also argued that even though, as a matter of law, the administrative law judge must consider the period through conclusion of the investigation, the administrative law judge may make a factual inference that because the consent order agreement involving the Novo respondents only covers up to July 1, 1994, complainant is not concerned about what happens after that date (Tr. at 2954-56).

In Pressure Transmitters the Commission stated that "the relevant period for determining [complainant's] lost sales in the absence of temporary relief is between March 19, 1990, when temporary relief, if any, would have been granted and October 20, 1990, when the investigation will conclude." Pressure Transmitters, Commission Opinion on Temporary Relief at 36. Thus, the period of time to be considered in calculating any irreparable harm to complainant ends on September 29, 1994, when final Commission action on permanent relief is due. The consent agreement between complainant and the Novo respondents does, however, reflect an attitude by complainant that activities undertaken after July 1 either will not cause irreparable harm or are worth the risk. Complainant is in the best position to judge what is and what is not important

to it. The terms of the consent agreement, which has been accepted into evidence as RBX-64 and which was voluntarily negotiated by complainant, does indicate the importance to complainant of post-July activities. Hence in considering any harm to complainant the consent order agreement will not be ignored.

B. Harm to Complainant In the Absence of TEO Relief

1. FDA Approval

Complainant's contention that it will suffer irreparable harm in the absence of temporary relief is necessarily premised on approval by the United States Food and Drug Administration (FDA) of BTG's pending New Drug Application (NDA) during pendency of this investigation (FF 273-276). Without such approval by the FDA, BTG is proscribed from selling, marketing, advertising, promoting or in any way commercializing its human growth hormone in the United States (FF 279).

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[19] HUMATROPE has received Orphan Drug status, which entitles Lilly to a seven year period of exclusivity during which time no other authentic human growth hormone for growth hormone deficiency may be marketed in the United States (FF 277). The seven year period of exclusivity for Humatrope is due to expire on March 6, 1994 (FF 277).

Complainant's argument that

is rejected as unsupported by the record.

Accordingly, the administrative law judge finds that

complainant will not suffer irreparable harm in the absence of temporary relief.[20]

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[20] BTG also argued

2. Marketing Ability of BTG

BTG argued that it will not cause complainant irreparable harm upon FDA approval of its NDA because

The record indicates that

The record also reflects

[21]

It is clear that

However, the administrative law judge finds

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[21] Moreover, although

3. Inventory of BTG

BTG has argued that it will

Complainant argued that

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In addition, contrary to complainant's assertion

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Accordingly, the administrative law judge finds that BTG

Moreover, even if

Thus the administrative law judge finds that

BTG will not inflict irreparable harm upon complainant in the absence of temporary relief.

4. Relative Competitive Positions

Complainant argued that upon FDA approval of its NDA, BTG will enter the U.S. hGH market with aggressively discounted prices, resulting in price erosion that will persist even after BTG is removed from the market, as well as loss of market share by Genentech; that such price erosion will result in

substantial and sustained loss of revenue by complainant; and that loss of market share will cause further loss of revenue (CB at 68-69). Such revenue losses, it was argued, will adversely affect

(CB at 69).

BTG argued further that complainant's size and strength in the market weigh against any irreparable harm (RB at 35-36); that any harm to complainant caused by BTG is compensable by money damages and are not irreparable (RB at 16-18); and that complainant's allegations of irreparable harm are too remote and speculative (RB at 19-21) and cannot be traced to BTG (RB at 33).

The relative market shares of the complainant and a respondent is a relevant factor in determining whether temporary relief should issue. Pressure Transmitters, Commission Opinion on Temporary Relief at 34. Here the record shows that complainant is the clear leader in the U.S. hGH market with

1992 sales of of hGH, and expected 1993 sales of of hGH (FF 326). Complainant has share of the U.S. hGH market (FF 325). In contrast, to date BTG has had no commercial sales of hGH and, indeed, without FDA approval of its BIOTROPIN NDA, BTG is proscribed from selling, marketing, advertising, promoting or in any way commercializing its hGH in the United States (FF 279). BTG's NDA remains pending before the FDA (FF 276) and,

In addition, the record demonstrates that the five elements of competition, in order of their importance to pediatric endocrinologists,[23] are: (1) service; (2) price; (3) reputation of the manufacturer; (4) product attributes; and (5) distribution (FF 332). The record further clearly establishes that complainant concentrates significant effort in developing its services, which services have enhanced complainant's reputation among pediatric endocrinologists (FF 339-342). Among the services complainant offers to pediatric endocrinologists is its National Cooperative Growth Study (NCGS), which collects information on the use and results of complainant's PROTROPIN, and on which complainant has spent to date, including in 1993 (FF 339). Complainant also provides seminars and one-on-one educational programs for physicians (FF 340). Complainant, in

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[23] Complainant's associate director of endocrinology and immunology, Bonnie S. Matlock,

addition, has a "specialized, highly trained sales force," including " clinical marketing specialists who make such frequent calls" (FF 341).

Complainant's Matlock testified that complainant's customers cite "the clinical expertise apparent in Genentech's clinical marketing specialists, its NCSG, and its recognized care in ensuring the quality and safety of its hGH . . . as important in their decision to use Genentech's hGH and is an important competitive consideration" (FF 342), and that a conservative statement of the costs of Genentech's sales and marketing activities related to its hGH sales in the U.S. are in 1991; in 1992; and between January and June of 1993 (FF 343). Also physicians hold complainant in very high regard and physicians "repeatedly have indicated that the reputation of the manufacturer of hGH is also an important attribute of competition in the U.S. hGH market" (FF 344).

[24] complainant's argument that BTG will successfully compete on the basis of discounted price is not supported by the record. Thus service, not price, is the most important factor to pediatric endocrinologists in determining which hGH product to purchase (FF 332) and pediatric endocrinologist are the most important customer group in the hGH market (FF 330). Despite Grabowski's testimony that complainant would be most vulnerable to price competition (FF 333), there is at least one incidence of pediatric endocrinologists, the most important customer group in the hGH market, overriding a Health Maintenance Organization's (HMO's) price-based determination to purchase a competitor's hGH product. In that instance, in May of 1993 Lilly outbid complainant for a contract with Kaiser, and Kaiser deleted PROTROPIN from its formulary and requested their physicians to prescribe Lilly's HUMATROPE. Yet, according to the manager of complainant's managed care department, Kenneth P. Gross, as a result of complainant's strong physician relationships, complainant has maintained of its Kaiser sales base (FF 346).

In addition, there was testimony by Grabowski that pediatric endocrinologists are hesitant to switch a patient from one brand of hGH to another during the course of treatment, particularly when there is danger that the patient may have to be switched again within a period of a few months (FF 347). As discussed supra, the administrative law judge has found that complainant is likely to prevail on the merits with respect to the '980 patent

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at issue in this investigation. That finding will be a matter of public record, and it is reasonable to assume that complainant's highly trained sales personnel will disseminate that information to pediatric endocrinologists and other decision makers within the U.S. hGH market as quickly as they are able.

Complainant's consent agreement with the Novo respondents suggests that complainant does not expect to be harmed by BTG after it enters the U.S. hGH market after June 1994. Complainant's Matlock testified that by the terms of their consent agreement with complainant, the Novo respondents are prohibited from entering the market before July 1, 1994; that complainant expects that the initial determination on permanent relief in this investigation will have issued by that time, with affirmative conclusions as to complainant's claims of infringement; and that final action by the Commission is due in September 1994 (FF 360). Matlock further testified that she believes that it is "unlikely" that the Novo respondents would enter the market after July 1 because "such a period is probably too short to make it worthwhile for Novo to attempt to establish relationships with potential customers and risk having its product taken out of the market three months later" (FF 360). When asked by BTG's counsel whether that reasoning was also applicable to BTG, Ms. Matlock testified at the hearing that

> "it is unlikely but not impossible that they [Novo] would enter the market. And I think the same situation holds true for BTG."

(FF 361). Ms. Matlock concluded that "the situation is fairly similar" (FF 361). Thus the administrative law judge finds that the terms of complainant's consent agreement with the Novo respondents and the testimony of Matlock concerning her expectations of BTG's post-July conduct

Based on the foregoing, the administrative law judge finds that the record as a whole establishes that BTG

is not likely to inflict irreparable harm on complainant by using discounted price during this time period.

C. Harm to BTG/Balance of Harms

As to the balance of harms between complainant and BTG, BTG indicates that the balance tips in BTG's favor. Thus BTG argued that a TEO should not issue because it is a small company

[25]

Complainant argued that BTG has

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[25]

BTG is a well financed and diversified company that would not be economically devastated by the inability to sell hGH in the United States during any TEO period.

BTG's Fass has been quoted in BTG's press releases as saying that "BTG's commercial success does not depend on any single product alone," and that "we believe that no single product reversal could at this

time seriously jeopardize BTG's projected success" (FF 390). Accordingly, and particularly in view of BTG's arguments that

the administrative law judge finds that BTG would not be significantly harmed by the loss of two months of expected U.S. sales.

The administrative law judge further finds that BTG

as a result of the issuance of any TEO.

As discussed, supra,

The administrative law judge also finds that BTG's arguments

are not

supported by the record.

Moreover, such arguments focus on harm that would result from adverse findings regarding the patents in issue,[26] irrespective of whether any TEO ultimately issues, and are not focused on any harm to BTG in the relevant time

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period because of an inability of BTG to sell hGH in the U.S. market. In past 337 investigations the harm to a respondent has been evaluated in terms of the economic effect on the respondent due to its inability to sell its product in the United States during the TEO period. For example, in Pressure Transmitters the Commission stated that the "loss of []% of [respondent's] business would have a significant adverse impact." Pressure Transmitters, Commission Opinion on Temporary Relief at 38. Similarly, in Certain Cellular Radiotelephones and Subassemblies and Component Parts Thereof (Radiotelephones), Inv No. 337-TA-297, Unreviewed ID (Aug. 9, 1989) the administrative law judge found that "[i]f respondents could not import or sell during the pendency of any temporary exclusion that may be ordered, they would likely lose sales, name recognition, and customer goodwill." Radiotelephones at 148. In this TEO proceeding BTG would not suffer an economic effect from its inability to sell hGH in the U.S. during the relevant time period.

Based on the foregoing, the administrative law judge finds that BTG would not suffer any harm if a TEO issued. Accordingly, the administrative law judge finds that the balance of harms tips in neither direction, having held that there would be no harm to complainant in the absence of temporary relief (supra at section VIII, B).[27]

D. Public Interest

Complainant argued that no public interest would be harmed by issuance

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[27] The Commission stated in Pressure Transmitters that "[a] finding that the balance of harms tips in favor of the party seeking preliminary injunctive relief is not a prerequisite to issuance of preliminary relief, however, but rather is one factor to be considered along with the public interest." Pressure Transmitters, Commission Opinion on Temporary Relief at 9. In Certain Circuit Board Testers the Commission found that the balance tipped in neither party's favor and denied the motion for temporary relief. Certain Circuit Testers, Commission Opinion on Temporary Relief at 3, 31.

of a TEO in this investigation. Complainant argued that there is a strong public interest in the protection of patent rights; that since BTG does not contribute to the hGH supply in the United States no shortage of hGH would result from issuance of a TEO; and that the public interest would be harmed by the failure to issue a TEO because is dependent upon protection of its commercially successful drugs (CB at 84-90). Complainant also argued that it has protected U.S. consumers in that its price has remained unchanged since 1985 despite an increasing consumer price index, and that complainant has successfully controlled diversion of hGH for unauthorized purposes (CB at 91-92). Complainant further argued that the threat to its NCGS in the absence of temporary relief is contrary to the public interest (CB at 91).

BTG argued that complainant's practice of price gouging, i.e. complainant's prices do not reflect the cost decrease of hGH production brought about by modern production methodology, implicates a public interest that weighs against issuance of TEO (RB at 43-44); that denial of complainant's Motion No. 358-1 would not affect U.S. production of hGH (RB at 44-45); that U.S. consumers would be harmed by issuance of a TEO because complainant's pricing is contrary to the public interest (RB at 45-46; RBR at 24-25) and because issuance of a TEO may harm BTG's ability to fund developments with respect to other drugs (RBR at 24); and that any affect on complainant's NCGS in the absence of a TEO is not relevant since the NCGS is merely a sophisticated marketing tool for complainant and does not benefit consumers (RBR at 25-26.

The staff argued that the public interests are not implicated by issuance of a TEO; that hGH treats non-life threatening condition; that no

patient's treatment would be interrupted by a TEO since BTG is not selling hGH in the U.S.; that Lilly and complainant can adequately supply U.S. demand for hGH;

The Federal Circuit has held that:

> Typically, in a patent infringement case, although there exists a public interest in protecting rights secured by valid patents [footnote omitted], the primary focus of the district court's public interest analysis should be whether there exists some critical public interest that would be injured by the grant of preliminary relief.

Hybritech, 849 F.2d at 1458. See also Pressure Transmitters, Commission Opinion on Temporary Relief at 38-39, quoting Hybritech.

Based on the record in this TEO phase of the investigation, the administrative law judge finds that no public interest would be harmed if a temporary exclusion order is issued. The record demonstrates that hGH is prescribed for the treatment of the condition of short stature due to growth hormone deficiency, which is a non-life threatening condition (FF 395); that since BTG is not currently selling BIOTROPIN in the United States, no patient's use of hGH would be interrupted by the issuance of preliminary relief excluding BIOTROPIN from the market (FF 396); and that complainant has adequate capacity to completely supply the United States market for hGH products (FF 397). Moreover, the record demonstrates that the FDA requires proof of safety and efficacy before it will approve a drug for commercial sale (FF 399), and that complainant's PROTROPIN has been approved by the FDA for use in treating growth hormone deficiency, and complainant's NUTROPIN has been

approved by the FDA for use in treating short stature associated with chronic renal insufficiency (FF 399). Thus the administrative law judge finds that there is no significant issue as to the safety and efficacy of complainant's hGH products.

BTG's argument that the public interest is implicated by complainant's history of price gouging is rejected as unsupported by the record. Thus the record indicates that prior to genetic engineering, the derivation of hGH from human cadavers was very difficult and costly, with the resulting product costing approximately $40,000 per gram (FF 400). Although Fass stated in an affidavit that complainant set the price for PROTROPIN at approximately 15% less than the price for naturally-derived hGH when it entered the market (FF 401), complainant's associate director of endocrinology and immunology projects, Bonnie S. Matlock, testified that when complainant entered the U.S. hGH market with PROTROPIN, it "established its price at a level approximately 25% below the then-prevailing price for hGH extracted from natural sources" (FF 402). In addition, complainant's price for PROTROPIN has remained unchanged since complainant entered the market in 1985 (FF 403), even though the Consumer Price Index for all prescription drugs has risen 80% since 1985 (FF 404). Thus, in relative terms, complainant's price for hGH has fallen by approximately 44% compared to the Consumer Price Index (FF 404). Moreover, Matlock predicts that, even if BTG does not enter the U.S. hGH market, prices will in 1994, 1995 and 1996 over current levels, for a (FF 405).

IX. Balance of the Four Factors

There are claims of three patents in issue. The administrative law judge has found that complainant is likely to succeed on the merits with

respect to the '980 patent, and that complainant has failed to show a likelihood of success on the merits with respect to the '832 patent, at the present time, and the '619 patent.

Of the investigations instituted with motions for temporary relief, only Radiotelephones involved multiple patents.[28] In Radiotelephones there were three patents at issue. In granting the motion for temporary relief in that investigation, the administrative law judge found that there was a "reasonably strong probability" of success on two of the three patents in issue, and that there was an "insufficient likelihood" that complainant would prevail regarding the infringement allegations as to the third patent. Radiotelephones at 141, 149.[29] The administrative law judge further found that the one of the two patents with respect to which complainant was likely to succeed on the merits concerned an "important part of the circuitry" in the products there at issue, which circuitry was found in both the complainant's and the respondents' products. Id at 147, n.22. Thus there is precedent for issuance of a TEO even though it is not found that complainant is likely to succeed on all of the patents in issue.

With respect to the remaining factors, the administrative law judge finds that complainant will not suffer irreparable harm in the absence of

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[28] Thus only one patent was at issue in each of Certain Crystalline Cefadroxil Monohydrate, Inv. No. 337-TA-293, Certain Doxorubicin, Inv. No. 337-TA-300, Certain Pressure Transmitters, Inv. No. 337-TA-304, Certain Woodworking Accessories, Inv. No. 337-TA-333, Certain Dynamic Sequential Gradient Compression Devices and Component Parts Thereof, Inv. No. 337-TA-335, and Certain Circuit Board Testers, Inv. No. 337-TA-342.

[29] In addition, the administrative law judge also found that complainant would suffer "immediate and substantial harm" in the absence of temporary relief and that respondent would likely suffer "substantial" harm if temporary relief was granted. Radiotelephones at 147-48.

relief and that, since respondent will suffer no harm if relief is granted, the balance of harms tips in neither party's favor. In addition, the administrative law judge finds that no public interest would be adversely affected if the requested relief is granted.

In Pressure Transmitters the Commission found that complainant was likely to succeed on the merits, but found that complainant would not be irreparably harmed in the absence of temporary relief. Pressure Transmitters, Commission Opinion on Temporary Relief at 33, 38. The Commission held that

> A showing of irreparable harm in the absence of relief is a requirement for issuance of a preliminary injunction in the Federal Circuit. Consideration of the balance of equities or the public interest, factors that counterbalance each other in this case, cannot overcome this deficiency. Because complainant failed to establish that it would be irreparable harmed in the absence of temporary relief, the Commission has determined to deny complainant's request for temporary relief.

Id at 40 (footnotes omitted). In this TEO proceeding complainant has shown a likelihood of success on the merits on one of the patents in issue but has failed to show that it will be irreparable harmed in the absence of relief. Accordingly, Motion No. 358-1 is denied.

X. Bonding

Complainant argued that a complainant's bond is discretionary, and that no such bond should be required of complainant in this TEO proceeding (CB at 92-94). Complainant argued further that if the Commission determines that a bond is necessary, the Commission should decrease the appropriate amount in the Commission's proposed rules to reflect the circumstances at hand in which sales revenues, particularly when the product is still relatively young, do not reflect the true status of the returns to complainant, i.e. "front-loaded costs" for the development of complainant's patent related products (CB at 94-96).

BTG argued that complainant's action is "plainly designed to harass" BTG; that complainant is unlikely to succeed on the merits; and that BTG will be harmed by issuance of temporary relief (RB at 46-47). Thus, BTG argued that complainant should be required to post as bond the full 100% of its sales revenues and licensing royalties to deter such "frivolous filings" (RB at 46; RBR at 27).

The staff argued that in practice the Commission has not followed the guidelines in the interim rules, but has opted for bonds of less than the minimum of 10% of sales revenues and licensing royalties set forth in the interim rules (SB at 63-65) The staff recommended that the administrative law judge apply the schedule set forth in the Proposed Final Rules Governing Investigations and Enforcement Proceedings Pertaining to Unfair Practices in Import Trade, 57 Fed. Reg. 52830, 52851 (Nov. 5, 1992), and impose a bond of $1,000,000 against complainant if the motion for preliminary relief is granted (SB at 65-66).[30]

Commission interim rule 210.24(e)(1)(iii), which covers the determination of whether to require complainant to post a bond, provides as follows:

> (iii) The factors the Commission will consider in determining whether to require a bond include the following:
>
> (A) The strength of complainant's case;
>
> (B) Whether posting a bond would impose an undue hardship on complainant;
>
> (C) Whether respondent has responded to the motion for temporary relief . . .;

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[30] The staff's recommendation, in so far as it applies the proposed Commission rules, is rejected. As of the institution of this investigation the Commission interim rules, not the proposed rules, were in effect.

(D) Whether the respondent will be harmed by issuance of the temporary exclusion order sought by the complainant;

(E) Any other legal, equitable, or public interest consideration that is relevant to whether complainant should be required to post a bond as a condition precedent to obtaining temporary relief (including the question of whether the complainant is using the temporary relief proceedings, or is likely to use a temporary exclusion order, to harass the respondents or for some other improper purpose).

In addition, Commission interim rule 210.24(e)(1)(v) provides that where domestic sales of the product in issue are not de minimis, "the amount of the bond is likely to be an amount ranging from 10 to 100 percent of the sales revenues and licensing royalties (if any) from the domestic product at issue . . . for the most recent fiscal year." The Commission has stated that the purpose of the complainant's bond is "to deter complainants from filing frivolous motions for temporary relief or using temporary relief as a means of harassing the respondent," and to overcome "Commission hesitation to grant temporary relief (e.g., in cases where the motion for temporary does not appear to be frivolous but the strength of the complainant's case is not overwhelming)." Summary of Public Comments on the Proposed Interim Rules, Overview of the Bonding and Forfeiture Processes, and Explanation of the Specific Interim Revisions to 19 C.F.R. Part 210, 53 Fed. Reg. 49120, 49121 Dec. 6, 1988).

As discussed in section VII, supra, the administrative law judge has found that complainant is likely to prove that the '980 patent at issue is valid and is infringed by BTG. In addition, although complainant has not shown that it is likely to succeed on the merits with respect to the '832 patent, at the present time, and the '619 patent, the administrative law judge

does not find that its assertion of infringement of those patents by BTG is "frivolous."

With respect to factor (B), complainant is the leader in the U.S. hGH market with 1992 U.S. hGH sales of some (FF 407). Imposition of an appropriate bond on complainant, in the event that the Commission grants Motion No. 358-1, would not be an undue hardship on complainant. As to factors (C) and (D), BTG has responded to Motion No. 358-1 and, as discussed in section VIII C, supra, the administrative law judge has found that BTG is not likely to suffer any harm if temporary relief is granted. Finally, with respect to factor (E), the administrative law judge finds that complainant's motion for temporary relief was not brought with the intent merely to harass BTG. There are no other public interests or other considerations relevant to the issue of whether complainant should be required to post a bond.

As set forth in Section IX, supra, the administrative law judge has found that complainant's Motion No. 358-1 for temporary relief should be denied because complainant has failed to show that it would be irreparable harmed in the absence of temporary relief. Should the Commission determine that the administrative law judge is wrong with respect to irreparable harm, and determine that complainant's position with respect to the '980 patent is weak, then a complainant's bond would be appropriate.

In past investigations the Commission has imposed bonds of an amount less than the 10 to 100% set forth in Commission interim rule 210.24(e)(1)(v). For example in Radiotelephones a bond of 5% was imposed in view of the large revenues involved and the strength of complainant's case. Radiotelephones, at 149-150. In Pressure Transmitters, a five percent bond was recommended by the administrative law judge. Accordingly, a bond of 5% would be appropriate in

this investigation.

FINDINGS OF FACT

A. Parties

1. Complainant Genentech is a Delaware corporation having its principal place of business at 460 Point San Bruno Boulevard, South San Francisco, California 94080 (CX-62).

2. Respondent Bio-Technology General Corp. is a Delaware corporation having its principal place of business at 70 Wood Ave. South, Metro Park Financial Center, 2nd Floor, Iselin, New Jersey 08830 (CX-48C, p. 2). The company's production activities are carried out through its wholly-owned subsidiary, Respondent Bio-Technology General (Israel) Ltd. in Rehovot, Israel (CX-195C, p. 2).

B. Products Involved

3. While the TEO proceeding relates to only certain process claims in issue and no product claims, the proceeding involves complainant's products NUTROPIN and PROTROPIN and BTG's BIOTROPIN. NUTROPIN and PROTROPIN are both brands of human growth hormone produced by recombinant DNA technology. NUTROPIN has 191 amino-acid residues, in a sequence identical to endogenous human growth hormone. PROTROPIN has the same molecular sequence, but it also has an additional N-terminal amino acid -- methionine (met) -- that NUTROPIN lacks (Matlock, CX-32 at 3).

4. BTG's human growth hormone product is known as BIOTROPIN (Fass, RB-2 at 5; Matlock CX-8 at 7).

C. The '619 patent

5. Claim 1 of the '619 patent reads as follows:

> A process for the production of a polypeptide comprising a preselected functional mammalian polypeptide or polypeptide

intermediate therefor in a microbial cell culture, said process comprising

(i) effecting expression of said polypeptide in a microorganism transformed with a replicable cloning vehicle comprising DNA encoding said polypeptide which DNA is under the control of an expression control region homologous to said microorganism; and

(ii) recovering the polypeptide from said cell culture.

(CX 2, col. 23, lines 40-50).

6. Claim 10 of the '619 patent depends from claim 1 and reads as follows:

The process of claim 1 wherein the polypeptide comprises a mammalian polypeptide and a selective cleavage site adjacent to the mammalian polypeptide.

(CX-2, col. 24, lines 3-5).

7. Claim 38 of the '619 patent depends from claim 1 and reads as follows:

The process of claim 1 wherein the polypeptide comprises human or bovine growth hormone.

(CX-2, col. 26, lines 4-5).

8. The '619 patent entitled METHOD AND MEANS FOR MICROBIAL POLYPEPTIDE EXPRESSION, was issued on June 22, 1993, to Keiichi Itakura and Arthur D. Riggs, and, on its face, is assigned to Genentech. The '619 patent expires on December 28, 1999, due to the filing of a terminal disclaimer (CX 2).

9. A peptide is a compound containing two or more amino acids in which the carboxyl (COOH) group of one acid is linked to the amino group (eg. NH_2) of the other, as for example in $H_2NCH_2CONHCH_2COOH$ (The Random House College Dictionary at 984 (1980)). Proteins can have a polypeptide structure (Fieser and Fieser "Organic Chemistry" at 450, D.C. Heath and Company (1950)).

10. The initial application Ser. No. 849,692 for the '619 patent was filed on Nov. 8, 1977. Thereafter continuation-in part Ser. No. 90,979 was

filed and the initial application abandoned. There followed the filing of five continuation applications, the last of which was Ser. No. 821,711 filed on Jan. 15, 1992. Four of those continuation applications were abandoned. Ser. No. 90,979 issued as U.S. Pat. No. 4,704,362 while the last filed continuation application Ser. No. 821,711 issued as the '619 patent (CX-2, title page, col. 1).

11. The '619 patent under the heading "Summary of Invention" states:

> According to the invention there is provided a recombinant plasmid suited for transformation of a bacterial host and use therein as a cloning vehicle, wherein plasmid comprises,
>
> a) A regulon homologous to the bacterial host in its untransformed state: and
>
> b) In reading phase with the regulon, a DNA insert coding for the amino acid sequence of a heterologous polypeptide, such that bacteria transformed by the plasmid are capable of expressing said amino acid sequence in recoverable form.

(CX-2, col. 4, lines 20-31).

12. The only specific experimental examples in the '619 patent are for the making of somatostatin and of insulin (CX-2, col. 10, lines 55 to col. 23, lines 37).

13. The material "human growth hormone" is sometimes referred to as hGH (Gottesman, RBX-4 at 2, 3).

14. Somatostatin has the following chemical formula:

(CX-2, Figure 1)

15. Somatostatin and insulin are not human growth hormones. Each is a fusion protein (Tr. at 2489).

16. Somatostatin is a functional mammalian polypeptide (Tr. at 2693).

17. Somatostatin is a very small protein. It has only 14 amino acids. It is therefore encoded in a short DNA sequence - a very short gene. The human growth hormone protein is much larger. It has 191 amino acids. It therefore has, a much larger gene. The larger a gene is, the harder it is to prepare synthetically (Falkinham, CX-7, QQ. 45, 46).

18. Genetic information is encoded on the double-stranded deoxyribonucleic acid molecule ("DNA" or "genes") according to the order in which the DNA coding strand presents the characteristic bases of its repeating nucleotide components (CX-2, col. 1, lines 27-29). A "gene" has been defined as the "basic unit of inheritance" (McGraw-Hill "Dictionary of Scientific and Technical Terms" at 796 (Fourth Edition)). Black's Medical Dictionary 36th Ed. (1990) at 297 states that genes, of which there are more than 100,000 in a human being, are the biological units of heredity and are arranged along the length of the chromosomes; and that there are dominant genes, recessive genes and sex-linked genes. The Columbia Encyclopedia 3rd Ed. (1963) at 805 states that a gene is the ultimate unit by which inheritable characteristics are transmitted to succeeding generations in animals and plants; that genes are contained by and apparently linearly arranged along the length of the CHROMOSOME; that the basic and universal chemical constituent of the gene is desoxyribonucleic acid, commonly called DNA; that it is believed that a gene is a giant molecule of nucleoprotein approximately the same size as a VIRUS; that genes were not visible until the development of the electron microscope,

although their function as units bearing a code for individual inheritable traits was deduced before then; and that it has now been established that each chromosome of each species has a definite number and arrangement of genes and that each gene has a specific and constant locus or position in the chromosome. The McGraw-Hill Encyclopedia of Science and Technology, Vol. 7 (1987) at 621 states as to the word "gene":

> The basic unit in inheritance. There is no general agreemment as to the exact usage of the term, since several criteria that have been used for its definition have been shown not to be equivalent.
>
> The nature of this difficulty can be indicated most easily after a description of the earlier position. The facts of mendelian inheritance indicate the presence of discrete hereditary units that replicate at each cell division, producing remarkably exact copies of themselves, and that in some highly specific way determine the characteristics of the individuals that bear them. The evidence also shows that each of these units may at time mutate, to give a new equally stable unit, which has more or less similar but not identical effects on the characters of its bearers. Each unit can be shown to occupy a specific locus in a chromosome, and the new units (alleles) to which it gives rise occupy the same locus. ...
>
> These hereditary units are the genes, and the criteria for the recognition that certain genes are alleles have been that they (1) arise from one another by a single mutative step, (2) have similar effects on the characters of the organism, and (3) occupy the same locus in the chromosome. It has long been known that there were a few cases where these criteria did not give consistent results, but these were explained by special hypotheses in the individual cases. However, such cases have been found to be so numerous that they appear to be the rule rather than the exception. ...
>
> Some authorities use the term gene to indicate the smallest unit of recombination. This is a logical procedure, but a somewhat inconvenient one operationally, since there is no method of determining when the limit of divisibility has been reached. Other authorities use the term to designate an area in a chromosome made up of subunits that are closely related in their action and that must be present in an unbroken unit to give their characteristic effect. This definition has the

> disadvantage of being rather indefinite, since intermediate conditions are known. ...
> One result of the varying definitions is a tendency to discard the word gene entirely and to substitute the terms muton (mutational unit), cistron (unit of biochemical activity), and recon (unit of genetic recombination) for it. It is probable that with increasing knowledge of the nature and properties of deoxyribonucleic acid (DNA) it will become possible to reach a more generally acceptable solution to the problems of terminology outlined above.
> ...

19. The "expression" of encoded information to form polypeptide involves a two-part process. According to the dictates of certain control regions ("regulons") in the gene, RNA polymerase may be caused to move along the coding strand, forming messenger RNA (ribonucleic acid) in a process called "transcription." In a subsequent "translation" step the cell's ribosomes in conjunction with transfer RNA convert the mRNA "message" into polypeptide. Included in the information mRNA transcribes from DNA are signals for the start and termination of ribosomal translation, as well as the identity and sequence of the amino acids which make up the polypeptide. The DNA coding strand comprises long sequences of nucleotide triplets called "codons" because the characteristic bases of the nucleotides in each triplet or codon encode specific bits of information (CX-2 col. 1, lines 31-42).

20. Three nucleotides read as ATG (adenine-thymine-guanine) can result in an mRNA signal interpreted as "start translation", while termination codons TAG, TAA and TGA can be interpreted as "stop translation." Between the start and stop codons lie the so-called structural gene, whose codons define the amino acid sequence ultimately translated. That definition proceeds according to the well-established "genetic code" which describes the codons for the various amino acids (CX-2 col. 1, line 47-57).

21. An operon is a gene comprising structural gene(s) for polypeptide

expression and the control region ("regulon") which regulates that expression (CX-2, col. 2, lines 15-17).

22. A promoter is a gene within the regulon to which the RNA polymerase must bind for initiation of transcription (CX-2, col. 2, lines 18-21).

23. An inducer is a substance which deactivates repressor protein, freeing the operator and permitting RNA polymerase to bind to promoter and commence transcription (CX-2, col. 2, lines 24-27).

24. A catabolite activator protein ("CAP") binding sinate is a gene which binds cyclic adenosine monophosphate ("c AMP") - mediated CAP, also commonly required for initiation of transcription. The CAP binding site may in particular cases be unnecessary (CX-2, col. 2, lines 28-34).

25. A promoter-operator system, as used in the '619 patent, is an operable control region of an operon, with or without respect to its inclusion of a CAP binding site or capacity to code for repressor protein expression (CX-2, col. 2, lines 38-42).

26. Cloning vehicle-a non-chromosomal double stranded DNA comprises an intact "replicon" such that the vehicle is replicated, when placed within a unicellular organism ("microbe") by a process of "transformation." An organism so transformed is called a "transformant" (CX-2, col. 2, lines 45-50).

27. A "plasmid", for the purposes of the '619 patent, is a cloning vehicle derived from viruses or bacteria, the latter being "bacterial plasmids" (CX-2, col. 2, lines 51-53).

28. The term "complementarity" is a property conferred by the base sequences of single strand DNA which permits the formation of double stranded DNA through hydrogen bonding between complementary bases on the respective strands. Adenine (A) complements thymine (T), while guanine (G) complements

cytosine (C) (CX-2, col. 2, lines 54-59).

29. Human growth hormone is an important protein which controls cellular growth and is secreted in the human body by the cells of the pituitary gland (Falkinham, CX-7, Q.7).

30. A cell is the basic unit of a living organism. Some organisms consist of only one cell -- for example, a microbial cell like *Escherichia coli* (*E. coli*). Other organisms are composed of many cells, for example, a human. In multi-cellular organisms, there are different types of cells which differ in their function(s). For example, certain cells in the pituitary gland produce inside the cell the precussor for human growth hormone. Every human cell has a nucleus which contains the information necessary for directing the cell's activities. This information is contained in a long, double stranded molecule called DNA (Falkinham, CX-7, QQ. 8, 9).

31. DNA is a polymer whose individual units are four "nucleic acids" (or "nucleotides") called adenine (A), thymine (T), cytosine (C), and guanine (G). These nucleic acids are linked together in a DNA strand. The beginning of the strand is called the "5' end" and the end of the strand is called the "3' end." A human's chromosomes are composed of DNA. It is the DNA molecule that is inherited from generation to generation (Falkinham, CX-7, Q. 10).

32. Each cell has the necessary and complex machinery required to synthesize proteins from DNA. Proteins are the agents which either make up the cell's structure or which perform its activities. To the latter category of proteins belong enzymes such as hormones. To synthesize a protein, first, there is the synthesis of an intermediate called "messenger RNA" (mRNA), which like DNA is a long linear molecule, but which is single stranded. Also like DNA, RNA is a polymer and has 5' and 3' ends. The individual units of RNA are

the "ribonucleotides" -- adenine (A), uracil (U), cytosine (C), and guanine (G). Uracil serves in RNA as thymine serves in DNA (Falkinham, CX-7, Q. 11).

33. The process of messenger RNA (or mRNA) synthesis is called "transcription" (Falkinham, CX-7, Q.12).

34. Messenger RNA, once produced, is transported from the nucleus to the cytoplasm where it associates with "ribosomes," particles within the cells. At the ribosome, the information encoded in the mRNA is translated into the amino acid sequence of a protein -- like human growth hormone and this process is called "translation" (Falkinham, CX-7, QQ. 13, 14).

35. Expression is the combined processes of transcription and translation and is the "decoding" of the DNA sequence into a protein sequence (Falkinham, CX-7, Q.15).

36. Proteins are composed of linear sequences of amino acids. The information for the linear sequence of amino acids in hGH is encoded by the linear sequence of nucleic acids in the hGH DNA. The amino acids are linked together by means of covalent bonds, called peptide bonds. Thus, proteins are called "peptides" or "polypeptides." Like DNA, the proteins have different ends. One end (the beginning) is called the "amino-terminal" (or "N-terminal") end, and the other end is called the "carboxyl-terminal" or ("C-terminal") end. Some proteins are secreted out of the cell. This process requires an amino acid sequence called a "leader sequence." By this process -- called "secretion" -- the protein is moved from inside the cell to outside the cell (Falkinham, CX-7, QQ. 15, 16).

37. A most common definition of a "gene" is a DNA sequence encoding a single protein. For example, one gene is for human growth hormone, another for insulin. In a human cell, the "nucleus" is in the center of the cell and,

within that nucleus, are "chromosomes". These chromosomes are large pieces of DNA that include individual genes linked together (Falkinham, CX-7, Q. 18).

38. The word "microbial" derives from the word "microbe," a group of organisms which can only be seen with a microscope. The title of the '619 patent, viz. "Method and Means for Microbial Polypeptide Expression," refers to the fact that a microbial cell, not a human cell, is used to express a polypeptide. In the '619 patent complainant first produces a gene for the polypeptide. Because the genetic code is essentially the same in all organisms, including mammals and microbes, that gene can be potentially transcribed and translated -- expressed -- in a microbial cell. Said gene is inserted ("ligated") into a carrier DNA molecule, called a cloning vehicle. One common cloning vehicle is a plasmid. The cloning vehicle with its inserted human growth gene can be introduced into a microbial cell (a process called "transformation" of the cell). If the gene is situated in the correct relationship with regard to sequences for expression, a microbial cell will produce the human growth sequence (Falkinham, CX-7, QQ. 19, 20).

39. Human growth hormone is not produced through the use of microbes unless the microbes are engineered (i.e., transformed) to do so because the microbial cell lacks the human growth hormone gene and hence is incapable of producing hGH itself as the human pituitary cells do in secretion. It is impractical to use human pituitary cells to produce hGH because human growth hormone cannot be produced in significant quantities from pituitary cells grown in the laboratory. One can make very large quantities of hGH through the use of microbial cells under conditions dictated by industrial production (Falkinham, CX-7, QQ. 21, 22).

40. The function of human growth hormone can be understood by

considering the results of a growth hormone deficiency -- dwarfism. Initially, the hormone was obtained from human cadavers. Pituitary glands were isolated, and the hGH was purified from the glands and injected into people. There never was enough to fulfill the need. It was also noticed that individuals treated with the cadaver-derived hGH were at risk for a disease that attacked the brain and was fatal -- called Creutzfeld-Jakob disease. This disease was caused by an infectious agent in the hGH derived from cadavers. It was for that reason that the FDA banned hGH (Falkinham, CX-7, QQ 23, 24, 25, 26).

41. DNA carries information for individual proteins. Part of DNA is the actual protein-encoding sequence called the "structural gene". The remaining DNA is a sequence necessary for production of the protein called a control sequence or "control region". The first step of protein synthesis uses one of these control region sequences -- the "promotor." The promoter is recognized by a component of the cellular machinery called "RNA polymerase," which synthesizes the mRNA. As the RNA polymerase moves along the DNA strand, the mRNA building blocks -- termed "ribonucleotides" -- are assembled into an mRNA strand. This process is referred to as transcription. The product of transcription -- the mRNA -- is a faithful copy of one of the two strands of DNA. After its completion, the mRNA moves from one cellular compartment, the nucleus, to another cellular compartment, the cytoplasm, where it associates with another component of the cellular machinery called a "ribosome." The ribosome associates with the mRNA at a specific site, the "ribosome binding site". In bacteria, that sequence is called the Shine-Delgarno sequence (after its discoverers). The ribosome moves along the mRNA, and the information encoded in the mRNA is translated into amino acids. By the

process called "translation" said amino acids are linked together through "peptide bonds" to produce the protein. Because the ribosome moves in one direction on the mRNA, a convention has developed to describe the location of sequences. For example, with respect to the ribosome-binding site (RBS), the structural gene to be translated is "downstream" (Falkinham, CX-7, QQ. 27, 28).

42. The information in DNA and its faithful transcript, mRNA, is in the form of three nucleic acid sequences called "triplet codons." Each triplet codon directs the cell to add a particular amino acid to a growing protein chain. The amino acid added is dictated by the cells "decoding" of the genetic code. Proteins are always initiated at a particular codon -- AUG in the mRNA (or ATG in the DNA). This codon encodes the amino acid methionine (or met). Once a protein is initiated at the AUG (ATG) codon, the sequence of nucleic acids in mRNA are read in threes (i.e., triplet codons), and the stepwise reading of the codons is referred to as being "in-phase". If there is a shift in the "reading phase," a whole different sequence of amino acids is incorporated into the protein. A shift in reading phase produces an entirely different product, Tyr-Val-Pro-Asn-Tyr (Falkinham, CX-7, QQ. 28, 29).

43. In the '619 patent, a plasmid was constructed and introduced into a microbial cell, in particular, into a strain of the microbe *E. coli*. The plasmid had a control region. This control region was from the microbial cell used as the host. The control region was not from a mammalian cell. In Example 1 of the '619 patent, the structural gene was the mammalian gene, somatostatin. There was also a portion of a different structural gene, b-galactosidase which was derived from *E. coli*. Between the fragment of the b-galactosidase gene and the somatostatin gene, there was a DNA triplet coding

for the amino acid methionine (met). That met served later to provide a target for the selective cleavage of the two portions of the fusion protein (i.e., the b-galactosidase fragment linked through peptide bonds to somatostatin). The invention involved moving the mammalian gene into the plasmid in a way that allowed Riggs and Itakura to exploit the presence of the microbial control region upstream of the inserted somatostatin gene. In the first example of the '619 patent, the inventors were able to produce functional somatostatin protein. Soon after that, they produced insulin (Falkinham, CX-7, QQ 38, 39).

44. The term "chemical synthesis" is one method for building a DNA chain. It involves linking the nucleic acids of the DNA chain together, one by one. Today, chemical DNA synthesis can be done by machine. In 1977, it was done by hand in the laboratory (Falkinham, CX-7, Q. 48).

45. Advances in biochemistry in "recent years", as that term was used on November 8, 1977 (the filing date of the original application for the '619 patent), have led to the construction of "recombinant" cloning vehicles in which, for example, plasmids are made to contain exogenous DNA. In particular instances, the recombinant may include "heterologous" DNA, by which is meant DNA that codes for polypeptides ordinarily not produced by the organism susceptible to transformation by the recombinant vehicle. Thus, plasmids are cleaved to provide linear DNA having ligatable termini. These are bound to an exogenous gene having ligatable termini to provide a biologically functional moiety with an intact replicon and a desired phenotypical property. The recombinant moiety is inserted into a microorganism by transformation and transformants are isolated and cloned, with the object of obtaining large populations capable of expressing the new genetic information (CX-2, col. 2,

lines 60-67, col. 3, lines 1-7).

46. A variety of techniques, as of November 8, 1977, were available for DNA recombination, according to which adjoining ends of separate DNA fragments are tailored in one way or another to facilitate ligation. The term "ligation" refers to the formation of phosphodiester bonds between adjoining nucleotides, most often through the agency of the enzyme T4 DNA ligase. Thus blunt ends may be directly ligated. Alternately, fragments containing complementary single strands at their adjoining ends are advantaged by hydrogen bonding which positions the respective ends for subsequent ligation. Such single strands, referred to as cohesive termini, may be formed by the addition of nucleotides to blunt ends using terminal transferase, and sometimes simply by chewing back one strand of a blunt end with an enzyme. Again, and most commonly, resort may be had to restriction endonuclease, which cleave phosphodiester bonds in and around unique sequences of nucleotides of about 4-6 base pairs in length (CX-2, col. 3, lines 22-40).

47. Prior to the filing of the initial '619 patent application on November 8, 1977, despite wide-ranging work in "recent years" (as that term is used in the '619 patent) in recombinant DNA research, few results susceptible to immediate and practical application emerged. This was proven especially so in the case of failed attempts to express polypeptide and the like coded for by "synthetic DNA", whether constructed nucleotide by nucleotide in the conventional fashion or obtained by reverse transcription from isolated mRNA (complementary or "cDNA") (CX-2, col. 3, lines 64-67, col. 4, lines 1-4).

48. The '619 patent, under the subheading "Background," does state that in "this application" the inventors describe what appears to represent the first expression of a functional polypeptide product from a synthetic gene,

"together with related developments which promise widespread application." The functional polypeptide product referred to is "somatostatin, (Guillemin U.S. Pat No. 3,904,594), an inhibitor of the secretion of growth hormone, insulin and glucagon whose effects suggest its application in the treatment of acromegaly, acute pancreatitis and insulin-dependent diabetes (CX-2, col. 4, lines 5-13).

49. Claim 1 requires a "replicable cloning vehicle comprising DNA" (CX-2) as a starting material. Referring to that starting material for the preparation of somatostatin, under the subheading "Experimental" (CX-2, col. 10, line 52), the sections "1. Construction of Somatostatin Gene Fragments" (col. 10) and "2. Ligation and Acrylamide Gel Analysis of Somatostatin DNA" (col 11) involves synthesizing the nucleic acid sequence that is the somatostatin gene. There are some 14 to 15 codons (Tr. 2493-94). As shown in said the section 2, the somatostatin DNA fragment was obtained and purified from unreacted and partially ligated DNA fragments (col. 12, lines 24-32).

50. Referring to section "3. Construction of Recombinant Plasmids" (CX-2 col. 12, line 37), Figure 4 of the '619 patent schematically depicts the manner in which recombinant plasmids comprising the somatostatin gene were constructed. As shown by Figure 4, the plasmid chosen for experimental somatostatin cloning was the parental plasmid pBR322, a small molecular weight plasmid carrying resistance genes to the antibiotics ampicillin and tetracycline. The ampicillin resistance gene includes a cleavage site for the restriction endonuclease Pst I. The tetracycline resistance gene includes a similar site for restriction endonuclease BamHI. An EcoRI site is situated between the ampicillin and tetracycline genes (CX-2, col. 12, lines 45-64).

51. The section titled "B. Construction of Plasmid pBH10" (col. 12, line

5) shows that plasmid pBH10 was obtained from pBR322 DNA and that plasmid pBH10 carried the fragment in the desired orientation, i.e. lac transcription going into the tetracycline gene (CX-2, col. 12, lines 67-68, col. 13, lines 1-45).

52. The section titled "C. Construction of Plasmid pBH20" (col. 13, lines 46) relates to modification of plasmid pBH10 to eliminate the EcoRI site distal to the lac operator. This plasmid pBH20 was next used to clone somatostatin gene. (CX-2, col. 13, lines 45-67, col. 14, lines 1-8).

53. The section titled "D. Construction of Plasmid pSOM 1" (col. 14, line 10) hows an attempted construction of plasmid pSOM 1. Plasmid pBH20 and somatostatin DNA were used. While the DNA sequence analysis of the clone carrying plasmid pSOM1 predicted that it should produce a peptide comprising somatostatin, no somatostatin radioimmune activity was detected in extracts of cell pellets or culture supernantants nor was the presence of somatostatin detected when the growing culture was added directly to 70 percent formic acid and cyanogen bromide. The absence of somatostatin activity in clones carrying plasmid pSOM 1 could result from intracellular degradation by endogenous proteolytic enzymes. Accordingly plasmid pSOM 1 was employed to construct a plasmid coding for a precursor protein comprising somatostatin and sufficiently large as to be expected to resist proteolytic degradation (CX-2, col. 14, lines 10-67, col. 15, lines 1-7).

54. The section titled "E. The Construction of Plasmids pSOM 11 and pSOM 11-3" (col. 15 lines 7-8) did involve construction of a plasmid in which the somatostatin gene could be located at the C-terminus of the beta-galactosidase gene, keeping the translation in phase. Such construction involved digestion of pSOM1 DNA. A resulting plasmid pSOM11 was used in the construction of

plasmid pSOM11-3. As reported in this section HindIII-BamHI double digestions indicated that only the clones carrying plasmids pSOM11-3, pSOM11-5, pSOM11-6 and pSOM11-7 contained the EcoRI fragment in a desired orientation. (CX-2 col. 15, lines 10-67, col. 16, lines 1-2).

55. The section titled "4. Radioimmune Assay for Somatostatin Activity" (col. 16, line 3) refers at col. 16, line 27 to the incubation of the mixture where one gets the expression called for in the first step (i) of claim 1 (Tr. at 2500, 2501). Critical to the formation of somatostatin is a formic acid-cyanogen bromide treatment and "[a]fter approximately 24 hr at room temperature, aliquots were diluted tenfold in water" (CX-2, col. 16, line 54, 55). It is this step that causes the somatostatin to form (Tr. at 2517, 2518).

56. With respect to step (ii) of claim 1 and the somatostatin experimental work reported in the '619 patent, said step (ii) is found in the section titled "Stability, Yield and Purification of Somatostatin" (CX-2, col. 18, lines 55-56) although that section also refers to the residue being cleaved with cyanogen bromide (CX-2, col. 19, lines 24-25). As to obtaining substantially pure somatostatin, reference is made to the recitation "[w]hen the product is again chromatographed on Sephadex G-50 and then subjected to high pressure liquid chromatography, substantially pure somatostatin may be obtained" (CX-2, col. 19, lines 30-32).

57. In the '619 patent the somatostatin structural gene is chemically synthesized. Thus the synthesized somatostatin gene was introduced into the bacterial host cell by inserting the gene into a plasmid containing a number of natural bacterial genes, including a fragment of the gene for a protein called beta-galactosidase (Falkinham, CX-7 at 17-18). There is expert

testimony that the somatostatin gene was inserted into the plasmid in such a way as to make a "fused" beta galactosidase/somatostatin gene, which would produce a hybrid beta-galactosidase/somatostatin protein (CX-2). This put the fused somatostatin under the control of the beta-galactosidase gene's control region (termed the "lac" control region) (Falkinham CX-7 at 17,18). A plasmid was constructed and introduced into a microbial cell, in particular, into a strain of the microbe E. coli. Id. at 16, 17. The plasmid thus has a control region which control region was from the microbial cell used as the host. Id. at 16, 17. The control region was not from a mammalian cell. Id. The structural gene was the mammalian gene somatostatin and there was also a portion of a different structural gene, beta-galactosidase which was derived from E. coli. and between the fragment of the beta-galactosidase gene and the somatostatin gene, there was a DNA triplet coding for the amino acid methionine (met) (Falkinham CX-7 at 16, 17).

58. The '619 patent states:

> While the developments described here have been demonstrated as successful with the somatostatin model, it will be appreciated that heterologous DNA coding for virtually any known amino acid sequence may be employed, mutans mutandis. Thus, the techniques previously and hereafter discussed are applicable, mutatis mutandis, to the production of poly(amino)acids, such as polyleucine and polyalanine; enzymes, serum proteins; analgesic polypeptide, such as B-endorphins, which modulate thresholds of pain etc. Most preferably, the polypeptides produced as such will be mammalian hormones or intermediates therefor. Among such hormones may be mentioned, e.g., somatostatin, human insulin, human and bovine growth hormone luteinizing hormone. ACTH, pancreatic polypeptide, etc. Intermediates include, for example, human preproinsulin, human proinsulin, the A and B chains of human insulin and so on. In addition to DNA made in vitro, the heterologous DNA ay comprise cDNA resulting from reverse transcription from mRNA. See, e.g. Ulrich et al, Science 196, 1313 (1977).

(CX-2, col. 6, lines 58 to 69; col. 7 lines 1-10).

D. Human Growth Hormone and the '619 Patent

59. Human growth hormone secreted in the human body by the cells of the pituitary gland consists of 191 amino acids and, with its molecular weight of about 21,500, is more than three times as large as insulin. Until the invention of the '980 patent, human growth hormone could be obtained only by the laborious extraction from the pituitary glands of human cadavers. The '980 patent states that the consequent scarcity of the substance coming only from human cadavers had limited its applications to the treatment of hypopituitary dwarfism, and even here reliable estimates suggest that human-derived hGH is available in sufficient quantity to serve not more than about 50% of afflicted subjects (CX-4, col. 3, lines 45-56).

60. Complainant has admitted that in the late 1970's, genes as long as that for human growth hormone, i.e. 191 amino acids and then three times that many, or 573 codons, were too long to synthesize and thus scientists turned to an alternate way of making genes, the so-called "cDNA" approach (CB at 9).

61. Complainant has admitted that "certainly" prior to the '980 and the '832 patents it was known in the prior art that human growth hormone, which is secreted in the human pituitary, consists of 191 amino acids and has a molecular weight of about 21,500 (Tr. at 2574-75).

62. Complainant has admitted that while the inventor Itakura in the '619 patent had used chemical synthesis to construct the somatostatin gene, the human growth hormone gene was much longer and more complex than somatostatin and thus the named inventors on the '980 and '832 patents decided that chemical synthesis alone was not feasible (Complainant's proposed finding 89).

63. A variety of considerations can influence distribution of codons for the end product as between synthetic and cDNA, most particularly the DNA sequence of complementary DNA determined as by the method of Maxam and

Gilbert, Proc. Nat'l Acad. Sci. U.S.A., 74, 560 (1977). Complementary DNA obtained by reverse transcription will invariably contain codons for at least a carboxy terminal portion of the desired product, as well as other codons for untranslated mRNA downstream from the translation stop signal(s) adjacent the caboxy terminus. The presence of DNA for untranslated RNA is largely irrelevant, although unduly lengthy sequences of that kind may be removed, as by restriction enzyme cleavage, to conserve cellular resources employed in replicating and expressing the DNA for the intended product. In particular cases, the cDNA will contain codons for the entire amino acid sequence desired, as well as extraneous codons upstream from the amino terminus of the intended product. For example, many if not all polypeptide hormones are expressed in precursor form with leader or signal sequences of protein involved, e.g., in transport to the cellular membrane. In expression from eukaryotic cells, these sequences are enzymatically removed, such that the hormone enters the piroplasmic space in its free, bioactive form. Thus the leader sequence is put there in nature to help the protein emerge from the mammalian cell after expression, and is clipped off automatically as the protein leaves the mammalian cell (Falkinham, CX-7 at 23). Microbial cells however cannot be relied upon to perform the clip off function, and it is accordingly desirable to remove sequences coding for such signals or leader sequences from the RNA transcript. In the course of that removal process the translation start signal is also lost, and almost invariably some codons for the intended product will be removed as well. A synthetic component of the quasi-synthetic gene product can return those later codons, as well as supplying a new translation start signal where the vehicle into which the hybrid gene will ultimately be deployed itself lacks a properly positioned

start. Elimination of the leader sequence from pregrowth hormone cDNA can be advantaged by the availability of a restriction site within the growth hormone-encoding portion of the gene (CX-3, col. 5, lines 13 to 50; CX-4, col. 5, lines 12 to 55).

64. Complainant's counsel at closing oral argument stated that the '619 patent does not enable the production of human growth hormone without its leader sequence; that the '980 patent which was not originally filed until July 5, 1979 requires the production of human growth hormone without the leader sequence and the leader sequence problem was not solved until the inventors of the '980 patent did their work with the semi-synthetic gene; and that whatever claim 38 covers it did not enable the solution of the leader sequence problem; and that "if your Honor wants to take that as invalidating claim 38, so be it" (Tr. at 2929).

65. There was the following statements made at the closing oral argument:

> JUDGE LUCKERN: But let me - - without solving that leader sequence problem, you can't get the human growth hormone?
>
> MR. HILLMAN: You can't get it without the leader sequence, That's right, your Honor.

(Tr. at 2929).

66. David V. Goeddel and Herbert L. Heyneker, the inventors of the '980 patent which was originally filed on July 5, 1979, approximately one year and one-half after the initial filing date of the '619 patent stated in the '980 patent:

> Until the present invention, human growth hormone could be obtained only by laborious extraction from a limited source - the pituitary glands of human cadavers. (CX-4, col. 3, lines 48-51).

67. Complainant's counsel represented that the "actual production of

human growth hormones without the leader sequence was not enabled back in 1977" or "as of the filing date of the '619 patent" (Tr. at 2590).

68. Complainant 's counsel represented that as of the filing date of the '619 patent one "couldn't produce it [human growth hormone] without the leader sequence" and that the '619 patent" doesn't teach you how to do it" and also to do it "was beyond the level of skill at that time" (Tr. at 2591).

69. Complainant's counsel represented that it is complainant's position that one could not from the '619 patent make a human growth hormone if one did not have the leader sequence on it and that the '619 patent says nothing about the leader sequence and the patent does not enable one to get rid of it (Tr. at 2591, 2592).

70. Claim 38 of the '619 patent does not say human growth hormone "without the leader sequence" nor does it say human growth hormone "withthe leader sequence" (CX-2).

71. Complainant represented that the prior art was "able to get human growth hormone with the leader sequence but not without the leader sequence" and that while the '619 patent does not teach a process for producing human growth hormone with a leader sequence, it would have been within the level of skill at the filing date of the '619 patent to get a human growth hormone "with a leader sequence" (Tr. at 2593, 2594).

72. The staff admitted that the chemical synthesis of the 191 codon gene was an "enormous engineering feat" and "was a monumental task in the industry" and that "the chemical synthesis synthesis for the somatostatin gene was not because Riggs and Itakura did it" (Tr. at 2599).

73. While the synthetic gene approach to actually express proteins for which the genes code has proved useful for "somatostation" and insulin as of

July 5, 1979, there were real difficulties in the case of far larger protein products, e.g., growth hormone, interferon, etc., whose genes are correspondingly more complex and less susceptible to facile synthesis. The inventors in the '980 specification disclosed that at the same time, it would be desirable to express such products unaccompanied by conjugate protein, the necessity of whose expression requires diversion of resources within the organism better committed to construction of the intended product (CX-4, col. 3, lines 4-12).

74. There is nothing in the '619 patent that teaches that when recombinant human growth hormone is produced in bacteria it will have a methionine on it (Tr. at 2569).

75. The '980 patent discloses:

> ... workers have attempted to express genes derived not by organic synthesis but rather by reverse transcription from the corresponding messenger RNA purified from tissue. Two problems have attended this approach. To begin with, reverse transcriptase may stop transcription from mRNA short of completing cDNA for the entire amino acid sequence desired. Thus, for example, Villa-Komaroff et al obtained cDNA for rat proinsulin which lacked codons for the first three amino acids of the insulin precursor. Proc. Nat'l Acad. Sci. USA 75 3727 (1978). Again, reverse transcription of mRNA for polypeptides that are expressed in precursor form has yielded cDNA for the precursor form rather than the bioactive protein that results when, in a eukaryotic cell, leader sequences are enzymatically removed. Thus far, no bacterial cell has been shown to share that capability, so that mRNA transcripts have yielded expression products containing the leader sequences of the precursor form rather than the bioactive protein itself. Villa-Komaroff, supra (rat proinsulin); P. H. Seeburg et. al. Nature 276, 795 (1978) (rat pregrowth hormone).
>
> Finally, past attempts by others to bacterially express hormones (or their precursors) from mRNA transcripts have on occasion led only to the production of conjugated proteins not apparently amendable to extra-cellular cleavage, e.g. Villa-Komaroff, supra, (penicillinase-proinsulin); Seeburg, supra (beta-lactamase-pregrowth

hormone).

(CX-4, col. 3, lines 13-41; CX-3, col. 3, lines 14-41).

76. There is no methionine on human growth hormone as it is secreted from the pituitary gland (Tr. at 2571).

77. A leader sequence is an amino-terminal sequence that is required for the secretion of the growth hormone molecule in mammals. This so-called leader sequence is not part of the final growth hormone product because it is removed by the mammalian cells. The leader sequence is removed when growth hormone is expressed in a mammalian cell, but the sequence is not removed when the hormone is expressed in E. coli. Just how to express a protein in a microbial cell without this leader sequence was a problem that plagued the scientific community. In fact, removal of the leader sequence from growth hormone was the topic of a discussion at the Benzon Symposium in Copenhagen. At this particular meeting, in August 1978, Howard Goodman of the University of California at San Francisco when asked how he would remove the leader sequence from an expressed growth hormone, answered that he had "very few good ideas" (CPX-28-2). Goodman didn't even think that the leader sequence necessarily had to be removed from the expressed growth hormone. He told the audience: "The question is whether it is ever going to be really necessary to take the hormone out of the fused protein" (CPX-28-2). Goeddel and Heyneker solved this problem by using a combination of cDNA and organically synthesized DNA as explained in their Nature paper (CPX-6-70). Thus they settled on the idea of getting most of the human growth hormone gene from cDNA and then organically synthesizing the growth hormone gene--without those sequences encoding the leader sequence. The method of combining a piece of cDNA and a piece of synthetic DNA is referred to as the semi-synthetic method (CX-3).

Goeddel and Heyneker recognized that, in removing the leader sequence, they removed the requisite initiator codon and that they needed to include this codon (the ATG codon for Met) in their engineered gene to guarantee translation of the hGH product. Complainant's approach essentially bypassed the growth hormone leader sequence (Kleid, CX-5 at 14 to 16).

77(a). Though microbial cells secrete certain proteins and those proteins contain the microbial equivalent of leader sequences, E. coli cannot recognize the mammalian leader sequences and remove them. Consequently, the mammalian proteins is produced with an amino-terminal leader sequence. Such leader sequence-containing proteins are nonfunctional (Falkinham, CX-7 Q. 57).

E. Technical Experts

78. Dr. Max Elliot Gottesman is the director of the Institute of Cancer Research at Columbia University (Gottesman, RBX-4 at 1).

79. Gottesman was qualified, on behalf of BTG, as an expert in molecular genetics and the production of recombinant expression vectors and their use to express polypeptides in bacteria (Tr. at 1700).

80. Dr. Joseph Oliver Falkinham is a tenured associate professor of microbiology in the Department of Biology at Virginia Polytechnic Institute and State University, Blacksburg, Virginia, (Falkinham, CX-7 at 1).

81. Falkinham was qualified, on behalf of complainant, as an expert in recombinant DNA technology, including cloning and the expression of eukaryotic genes and bacteria and subsequent processing of the expressed material (Tr. at 982, 983).

82. Dr. Michael J. Chamberlin is a professor of biochemistry and molecular biology at the University of California, Berkeley (Chamberlin, CX-224 at 1).

83. Chamberlin was qualified, on behalf of complainant, as an expert in recombinant DNA technology, including cloning and the expression of eukaryotic genes and bacteria and subsequent processing of the expressed material (Tr. at 521).

84. Dennis Kleid is a senior scientist and patent agent with complainant's legal department (Kleid, CX-5 at 1).

85. Dennis Kleid was qualified, on behalf of complainant, as an expert in recombinant DNA technology, including cloning and expressions of eukaryotic genes in bacteria and subsequent processing of the expressed material (Tr. at 358).

Level of Ordinary Skill In The Art

86. With respect to the '619 patent, complainant proposed:

> CFF150. Based on testimony from both BTG and Genentech, one with ordinary skill in the art would have a Ph.D. in a field relevant to biotechnology (such as genetics or molecular biology) and at least a few years experience working in a laboratory in the field.

(Kleid, Tr. at 425-426, Chamberlin, Tr. at 570-572; Falkinham, Tr. at 1086-1087). In response BTG stated:

> CFF150. BTG objects to Genentech's proposed finding of fact CFF150 as inaccurate and unsupported by the record. Genentech's proposed level of ordinary skill in the art is inaccurate. BTG directs the Administrative Law Judge to RT272-273.

BTG's RT272 and RT273 read:

> RT 272. A person of ordinary skill in the art is someone with a Ph.D. in molecular cloning and molecular biology with 2 or 3 years of additional experience (Chamberlin, Tr. at 571).
>
> RT 273, Dr. Gottesman would qualify as somebody of ordinary skill in the general area of molecular biology and gene expression (Chamberlin, Tr. at 5720573).

Complainant, responding to RT272, stated:

CRFF371. Proposed finding RT 272 is incorrect. See CFF150; 219; 360. In addition, this proposed finding incompletely summarizes Dr. Chamberlin's testimony. He testified that a Ph.D. in other fields, such as chemistry or biochemistry, would be appropriate (Chamberlin, Tr. at 571).

Based on the testimony of the expert witnesses (Kleid, Falkinham, Chamberlin and Gottesman) and the administrative law judge's observation of those witnesses, the administrative law judge finds that the level of ordinary skill in the art, with respect to the claims in issue of each of the '619, '832 and '980 patents, would be a person who would have a Ph.D. in genetics, molecular biology, chemistry or biochemistry with at least a few years additional experience in genetics or molecular biology.

G. Validity of Claims 1, 10 and 38 of the '619 Patent Under 35 U.S.C. §103

87. The Struhl et al reference is an article titled "Functional genetic expression of eukaryotic DNA in Escherichia coli published in Proc. Natl. Acad. Sci. USA Vol. 73, No. 5, pp. 1471-1475 (May 1976) (RBX-122). The reference concerned a polypeptide from a unicellular organism, a yeast cell, which is very different from a mammal. Also Struhl et al do not prove that a yeast polypeptide was expressed. The authors at 1475 concede that their results might be explained by a phenomenon other than expression of a polypeptide: "[a]lthough we have not yet excluded the possibility of suppression, we believe it more likely that the yeast DNA . . . codes for the structural gene . . ." (Chamberlin, CX-227 at 1-2).

88. The Itakura reference (RBX-123) is an abstract published from the 26th International Congress of Pure and Applied Chemistry (Tokyo, Japan, September 4-10, 1977) (Kleid, CX-231 at 1).

89. With reference to the dated of the somatostatin '619 invention, in a memo from Dr. Art Riggs communicating results to Dr. Levine at the City of

Hope (CX-235), Riggs says "[w]e got positive results on ." There is also a Genentech notebook documenting the results that Riggs refers to in his memo (CX-234). Genentech notebook 1/24 dated August 1977 records the results from the scintillation counter on page 5 as follows:

Results: has SS.

show negative results.

(CX-234, p. 5) (Kleid, CX-5 at 2, 3).

H. Human Growth Hormone and the Accused BTG Process

90. Pertinent to BTG's process in issue is the following portion of BTG's New Drug Application for BIOTROPIN (RBX-101 Bates 000305 to 000307; CPX-26, Tab 21, Bates 000305 to 000307).

91. **[THERE IS NO FINDING 91]**

92. BTG's New Drug Application for BIOTROPIN

93. BTG's expert

A. I think they were careless and they should --

JUDGE LUCKERN: But you agree, That is correct.

THE WITNESS: Yes. Oh, yes. They have but it's an incorrect usage.

BY MR. HILLMAN:

Q. And the inventors in the '980 patent did the same thing as BTG did in what you call the incorrect usage, isn't that true, Sir?

A. They did more than that. They are confusing Met-hGH with human growth hormone and they're not the same. At no time in this ['980] patent is human growth hormone expressed.

* * *

Q. Right. So what they're telling us is that the expression product is going to have the Met on it; right?

A. Yes, but they expect it to be removed.

Q. But the expression product is going to have it on there; right?

A. That's correct.

Q. And then is claim 2 [of the '980 patent] they refer to the expression product as human growth hormone, don't they?

A. Yes, they do.

Q. And doesn't that mean, therefore, that if we construe the claim in light of what they tell us about the meaning of these words in the specification, that by the inventors lexicography, human growth hormone includes Met-hGH?

A. That may be a lex -- what is that word? I'm sorry.

JUDGE LUCKERN: Lexicography.

THE WITNESS: Lexicography. That's tough. That may be their lexicography but it is not correct usage.

BY MR. HILLMAN:

Q. But you agree that it is their lexicography?

A. Apparently it is. That they believe Met-hGH and hGH are the same.

Q. So if we construe these claims in terms of the inventors' lexicography rather than the one that you say is correct, then much of your non-infringement argument vanishes, doesn't it, because it's all based on your glossary which is inconsistent with the inventors' glossary?

A. But that boils down as to whether or not there's a different between Met-hGH and hGH and there is a different. [sic] If you're --

* * *

MR. HILLMAN: Your Honor, I'd like an answer to that question.

JUDGE LUCKERN: Read -- can you answer the question? Can you answer the question?

THE WITNESS: Yes. As I understand the question I'm being asked to accept the inventors' lexicography although I don't agree with what that lexicography is and I don't believe that lexicography is the correct usage for either Met-hGH or hGH, as I pointed out at the beginning of my testimony.

BY MR. HILLMAN: Let me clarify, Doctor. I'm not asking you to accept the inventors' lexicography. What I'm asking you is this. If we apply the inventors' lexicography, no mater how painful it may be to you, isn't it true that most of your non-infringement analysis vanishes?

THE WITNESS: I think if I accept claim 2 in terms of how the inventors are using the words, which I think is incorrect, that would weaken the case against non-infringement, but I can't accept that lexicography.

(Gottesman, Tr. at 1842, 1843).

94. U.S. Patent No. 4,599,197 ('197 patent) titled "Purification and Activity Assurance of Precipitated Heterologous proteins" issued July 8, 1986 to Ronald B. Wetzel. It was based on Ser. No. 625,677 filed June 1, 1984 and is assigned on its face to "Genentech Inc." Ser. No. 615,677 is a continuation of Ser. No. 452,187 filed December 22, 1982 (RBX-211).

95. Lines 8 to 44 of col. 1 and lines 6 to 33 of col. 23 of the Wetzel '197 patent (RBX-211) read:

BACKGROUND OF THE INVENTION

Recombinant DNA technology has permitted the expression of exogenous or foreign (heterologous) proteins in bacteria and other host cells. Under some conditions, and for some proteins, these heterologous proteins are precipitated within the cell as "refractile" bodies. The present application concerns procedures for recovering these heterologous proteins and for restoring them, if necessary, to their active forms.

A large number of human, mammalian, and other proteins, including, for example, human growth hormone, (hGH) bovine growth hormone (bGH) and a number of interferons have been produced in host cells by transfecting such cells with DNA

encoding these proteins and growing resulting cells under conditions favorable to the expression of the new heterologous protein. Viral coat proteins, such as capsid proteins of foot and mouth disease (FMD) virus and the surface antigenic protein hepatitis B virus (HBsAg) are still other examples of heterologous proteins which have also been produced in suitable recombinant DNA engineered hosts. The heterologous protein is frequently precipitated inside the cell, and constitutes a significant portion of the total cell protein.

In a large number of important cases, such as those of hGH, porcine growth hormone (pGH), bGH, FMD, and fibroblast interferon (FIF), it has been observed that the heterologous proteins produced are not only present in large quantity, but are precipitated within the cell in the form of "refactile" bodies. The term "refractile" is used because these bodies can actually be seen using a phase contrast microscope. Under magnifications as low as 1000 fold, these precipitated protein bodies appear as bright spots visible within the enclosure of the cell.

* * *

Recombinant DNA E. coli K12 cells carrying human growth hormone gene (strain W3110/p107) as described in U.S. Pat. No. 4,342,832 were grown in fermenter and harvested, and refractile particles isolated according to the procedure described in Example 1.

The particles showed a protein band corresponding to a molecular weight standard of 22,000 daltons on 2-mercaptoethanol SDS-PAGE. A densitometer scan of the gel showed the amount of this protein was over 90 percent of the total protein in the refractile particle preparation, and the identify of this protein as human growth hormone was verified by Western blot. The yield of refractile particles was about 10-20 mg per gram of wet cell paste.

FIG. 4A shows the refractile hGH containing bodies in a suspension of the pellet from the first spin.

FIG. 4B shows the results of SDS PAGE performed on killed (with acid) and unkilled cells from this preparation. The band corresponding to hGH in pellet from killed cells is enhanced. [col. 23, lines 6-33] [Emphasis added]

96. BTG's expert Gottesman testified (Tr. at 2232 to 2234):

* * *

Q Okay. Now, I'd like you to look at RBX 211 which Mr.

White questioned you about. That's the Wetzel patent. Do you have that there, sir?

* * *

Q I'd like you to look in Column 1 of that patent at line 18 or 19, 19 and 20 actually. You see it says there human growth hormone (hGH) [see preceding finding and the emphasized portion of the second paragraph]?

* * *

Q Column 1, lines 19 and 20. Of course, you can read any part of this you want. Take your time. But my question is going to be related to the words human growth hormone (hGH) that appear in lines 19 and 20. Do you see that?

A I see that, sir.

Q Is that referring to the 191 amino acid polypeptide or the 192 amino acid polypeptide?

A That's referring to the 192, sir.

Q That's inconsistent with your glossary definition --

A That's correct.

Q -- of human growth hormone, isn't it?

A It is not authentic human growth hormone.

Q And then again down in line 34 of Column 1 of that same patent [see preceding finding and the emphasized portion of the third paragraph] it says hGH again. Is that another usage that is inconsistent with your definition of human growth hormone?

A Yes, sir. That's referring to the 192 amino acid, polypeptide.

Q And then in Column 23, doctor, at lines 19 and 20, there's another reference to human growth hormone [see preceding finding and emphasized portion in col. 23]. Do you see that?

A Yes, sir.

Q What does that refer to, 191 or 192?

A That's 192, sir.

Q And that's also inconsistent with your glossary definition isn't it?

A Yes, sir.

97. By letter dated January 20, 1992 (CX-139) to Congressman Levine of the US House of Representatives from BTG's Sim Fass, Fass stated in part:

> The use of human growth hormone in the treatment of osteoporosis, burns, fractures, muscle mass atrophy, prevention of body mass wasting (e.g., cancer and AIDS) - newer areas being clinically explored - could again add [sic] hundreds of thousands of affected individuals and define incremental human growth hormone market potentials in the hundreds of millions of dollars.
>
> The attached article addresses the issue of these incremental markets. With worldwide sales exceeding $700 million, human growth hormone has emerged as the biotechnology industry's most successful product to date. The U.S. portion already exceeds $200 million and will grow dramatically in the coming years. Its designation as an "orphan" indication and/or market is nothing short of a mockery of original Congressional intent.
>
> Eli Lilly's Orphan Drug status has greatly disadvantaged Bio-Technology General Corp. The Company's investment in the product is approximately $10 million, with no expectation to recoup such investment before 1995 or 1996. Although we are actively supporting the Orphan Drug amendments submitted by Senators Metzenbaum and Kassenbaum, as well as Representative Studds, likelihood of the Presidential veto, if passed, remains high.
>
> We wish, therefore, to explore the possibility of a private bill that would exempt Bio-Technology General Corp. from the marketing exclusion mandated by the Orphad Drug Act.

98. The attached article (CX-139), referred to in Fass' letter (CX-139), stated in part:

> Genentech's genetically engineered human growth hormone was approved in 1985 for marketing in the U.S. and several other countries. Although this early genetically engineered product differed slightly from the natural, extracted product - the difference probably being responsible for eliciting an immune response in up to 40 percent of treated kids - it filled a crucial need at a critical time.
>
> Since that first approval, Lilly has subsequently

> received approval for genetically engineered authentic hGH (i.e., fully identical to the pituitary-extracted hormone) for which the immune response has been reduced to approximately 7 percent. Lilly's approval for the authentic hormone, as was Genentech's approval for the non-authentic hormone, was coupled to the granting by the U.S. Food & Drug Administration (FDA) of Orphan Drug Status, which provides exclusivity to companies that are first to develop therapeutic treatments for rare diseases. But Orphan Drug Status legally prevents the FDA from granting additional marketing approvals to other companies that have developed their own genetically engineered hGH's. As a result, companies like Bio-Technology General Corp./Du Pont (with a product exhibiting a zero immune response incidence), Serono and Nordisk have been blocked from competing in this growing health care sector. [Emphasis added] [Bates 933]

BTG's Gottesman testified (Tr. at 2236 to 2239).

Q Now, you've studied Genentech's human growth hormone products, have you not? In connection with this lawsuit or this proceeding.

A I've studied the patents?

Q No, the products. Do you know what they are?

JUDGE LUCKERN: Genentech's.

BY MR. HILLMAN:

Q Genentech's.

A Yes, I know what they are.

Q The one that's on the market now, the only one, is Protropin, correct?

* * *

BY MR. HILLMAN:

Q Is there any doubt in your mind, sir, that the genetically engineered human growth hormone product of Genentech that was approved in 1985 for marketing in the U.S. is PROTROPIN?

A It is PROTROPIN. It has 192 amino acids.

Q So this is another example of a document [CX-139] that uses the words human growth hormone in a manner that's inconsistent with your glossary, isn't that right?

A No, sir. It is not right.

Q Why not?

A Because it modifies human growth hormone with genetically engineered and then goes on in the next sentence to explain why that modification is important because --

JUDGE LUCKERN: Where are you reading from?

THE WITNESS: In this paragraph Genentech's genetically engineered human growth hormone [see preceding finding, first complete paragraph].

JUDGE LUCKERN: Okay, I'm with you now.

THE WITNESS: So genetically engineered modifies human growth hormone and it modifies it in a significant way because in the next sentence although this early genetically engineered product differed slightly, he explains what he means when he says genetically engineered and then goes on to say that this difference in terms of amino acids is slight, but in terms of biological side reactions is critical. Having elicited 40 percent of the patients immune response.

* * *

BY MR. HILLMAN:

Q You've given testimony about PROTROPIN have you not?

A I've given testimony about PROTROPIN.

Q And you've given testimony about NUTROPIN, right?

A NUTROPIN, yes I have. Yes.

Q And both of those are genetically engineered human growth hormones sold by Genentech, manufactured by Genentech, is that correct?

A One is authentic and one is not authentic. One is 192 amino acids.

Q But would you agree that they are both genetically engineered human growth hormone?

A Not if what's meant by genetic engineering is to modify human growth hormone in a way that it is different from authentic human growth hormone. And if it is not and the NUTROPIN is authentic human growth hormone and PROTROPIN is not authentic human growth hormone.

99. CX-62 is Genentech's 1992 Annual Report. BTG's expert Gottesman testified (Tr. at 2240 to 2253):

Q All right. This is, you can see that this is a Genentech annual report, can you not?

A It says "1992 Annual Report, Genentech, Incorporated," yes, sir.

Q Okay, and I would like you to look at -- I don't see any page numbers on here, so look at the fourth page, counting each side as a page, the page that is headed "Highlights."

A Highlights? Highlights, yes, I see that, sir.

* * *

Q It's the page that has number 2 on it, and it's headed "Highlights." Then down at the bottom of the first column there's a heading, "Marketed Products." Do you see that?

A Yes, sir.

Q And the first one that's mentioned is PROTROPIN, called Protropin, and then a parenthetical remark, "human growth hormone," right?

* * *

Q Do you see that, doctor?

A Yes, I do.

Q Would you agree that PROTROPIN is human growth hormone?

A What this refers to is PROTROPIN human growth hormone. It's all one phrase, "PROTROPIN human growth hormone," and that is not human growth hormone.

Q So PROTROPIN is not human growth hormone. Is that your position?

A PROTROPIN is not human growth hormone. It's 192 amino acids, sir.

Q Is NUTROPIN human growth hormone?

A NUTROPIN has 191 amino acids. It is human growth hormone.

Q And that's referred to at the top of the next page as

being human growth hormone, right?

A The top of the next page?

JUDGE LUCKERN: The next page is page 3, under "Product Development." That's I think what you're referring to, isn't it correct, Mr. Hillman?

MR. HILLMAN: That's correct, Your Honor.

JUDGE LUCKERN: Well, do we have an answer?

THE WITNESS: Yes.

JUDGE LUCKERN: Yes, the witness said yes. Go ahead.

BY MR. HILLMAN:

Q Doctor, does BTG have a genetically engineered human growth hormone?

A They obtained their human growth hormone by genetic engineering.

Q Would you call their human growth hormone genetically engineered human growth hormone?

A If by that, sir, you mean that it implies that it is not authentic, then I would not characterize it. It is authentic.

Q Well, going back to Exhibit 139-C, CX139-C --

* * *

Q Now let's go back to Exhibit 139, CX139 [See preceding finding].

A Yes, sir.

Q When I asked you about this exhibit before, I referred you to the phrase in the fourth line that referred to Genentech's genetically engineered human growth hormone [Bates 933 of CX-139]. Do you see that phrase again?

A Yes, sir, I do.

Q Now what do you think the words "genetically engineered" in that line mean?

* * *

Q What do you understand those words to mean, "genetically

engineered"?

A That they involve the use of recombinant DNA technology.

Q Okay. Now with that meaning of genetic engineering, of "genetically engineered," would you agree that the sentence on page 933 of this exhibit [CX-139] that says, "Genentech's genetically engineered human growth hormone was approved in 1985 for marketing in the U.S. and several other countries," would you agree that in that sentence the words "human growth hormone" are being used to refer to the 192 amino acid product and in a manner inconsistent with your glossary definition?

* * *

THE WITNESS: This is a letter, as I understand it, to a Congressman who I assume is not a trained scientists [sic]. It's a letter to Congressman Mel Levine.

And Dr. Fass is trying to explain what BTG has and what Genentech has without using excessive scientific terminology.

He doesn't want to use Met-hGH. He doesn't -- I assume, you know. The letter is not meant to be at that level. But if you're looking, throughout the letter, it's clear in the letter that he makes a distinction between what Genentech's product is and what BTG's product is or what authentic human growth hormone is.

Genentech's is referred to genetically engineered human growth hormone and Lilly's product and BTG's product, for that matter, is referred to as genetically engineered authentic human growth hormone.

So I see a very clear distinction here. He's using modifier words instead of Met-hGH and hGH, presumably because this is a letter to a non-specialist.

JUDGE LUCKERN: Go ahead, Mr. Hillman.

BY MR. HILLMAN:

Q But you do agree that in using the words human growth hormone to refer to Genentech's product, he's using it in a manner different than your glossary; correct?

* * *

Q You do -- do you understand that the usage of human growth hormone in this letter to refer to Genentech's product is inconsistent with your glossary definition, even though it's written to a non-scientist?

A I think as I said, I could only repeat myself. That it doesn't stand in isolation. It's referred to as genetically engineered human growth hormone and contrasted with genetically engineered authentic human growth hormone.

Q And they're both called human growth hormone with those modifiers; correct?

A I think I've answered that question already, sir.

100. BTG's expert Gottesman testified (Tr. at 2248-49):

> Q Doctor, you have offered us a glossary definition of human growth hormone. In your opinion, has the meaning of the term "human growth hormone" changed between 1979 and today?
>
> A No, human growth hormone is 191 amino acids, sir.
>
> Q Has the meaning changed, sir?
>
> A No, sir.
>
> Q Okay, so that if we were able to ascertain the meaning in 1992 with certainty, we would know that that's what it meant in 1979, as well, Isn't that correct?
>
> A It has not changed, sir.

101. All mamammlian proteins expressed in bacteria will begin with a met (Falkinham, CX-7, para. 78). The '980 patent makes this explicit at col. 7, lines 52-57 (CX-4) which reads:

> Of course, the expression product will in every case commence with the amino acid coded for by the translation start signal (in the case of ATG-f-methionine). One can expect this to be removed intracellularly, or in any event to leave the bioactivity of the ultimate product essentially unaffected.

(Falkinham, CX-228-1 at 1-2).

102. Exhibit RBPX-100 illustrates a properly folded active human growth hormone protein molecule. The model shows two disulfide bridges that permit the protein to fold properly. Those disulfide bridges are represented by

rubber bands that connect cystine residues, and as a result of those bridges, the polypeptide chain is kept in a certain configuration that is essential to the activity of the hormone. The cystines in RBPX-100 are shown as yellow balls. The ashtrays of RBPX-100 are intended to illustrate the binding domains of the receptor to which human growth hormone binds. It's the binding to this receptor that is essential for the response of the cells to human growth hormone. Binding of human growth hormone to its cellular receptor is an extremely complex event that requires two receptor extracellular domains interacting with one molecule of appropriately folded human growth hormone. The proper folding of the hormone is essential for its interaction with receptor and that would be the case for the human growth hormone as well. Met-HGH aggregated, improperly folded, insoluble and reduced will not interact with its receptor. Only the appropriately folded disulfide bonded, soluble form of human growth hormone would interact with its receptor to trigger a cellular response and thus be biologically active (Gottesman, RBX-4, QQ. 12, 13).

103. Disulfide bridges in RBPX-100 are known as disulfide bonds (Gottesman, RBX-4, Q. 14).

104. Disulfide bonds are not formed in E. coli, which has a reducing atmosphere that prevents the formation of disulfide bridges. Thus biologically active human growth hormone cannot be expressed in E. coli because without the formation of the disulfide bonds, the polypeptide backbone would not have the appropriate configuration. Those bonds are essential for folding the polypeptide into the active form of the hormone (Gottesman, RBX-4, QQ. 15, 16).

105. RBPX-101 is intended to illustrate the primary expression product

of BTG's Met-hGH clone in E. coli. What it illustrates is a molecule which has no particular secondary or tertiary structure. It is, in fact, part of an aggregate and is insoluble. Also shown in this model is the N-terminal methionine (met) which is present in the initial expression product and is retained in this aggregated form of met-hGH. This molecule is improperly folded and is reduced. There are no disulfide bridges in this initial product which will not interact with the human growth hormone receptor. The initial product is neither soluble nor properly folded and it retains the N-terminal methionine. The E. coli methionine-removing enzymes do not work on this product and other steps are required to remove the methionine to form a biologically active form of human growth hormone outside E. coli (Gottesman, RBX-4, Q. 19).

106. Met-hGH is a polypeptide which is one hundred and ninety-two amino acids long and has an additional methionine residue at the N-terminus of the sequence of human growth hormone. While one form of Met-hGH is expressed this form of Met-hGH has no biological activity. It is reduced and insoluble and is present as an aggregate within inclusion bodies in the E. coli cells. A second form of Met-hGH which has disulfide bridges and is soluble

(Gottesman, RBX-4, Q. 20).

107. The following finding corresponds to BTG's proposed finding 5 and was not objected to by Genentech nor the staff:

> Met-hGH is a polypeptide which is one hundred and ninety-two amino acids long and has an additional methionine residue at the N-terminus of the sequence of human growth hormone. Met-hGH expressed in E. coli in quantity is biologically inactive, insoluble,

improperly folded, and reduced (i.e. lacks the disulfide bonds required for biological activity). Met-hGH can be rendered biologically active, soluble, properly folded, nonreduced (i.e. disulfide bonds present) by procedures carried out outside E. coli. (RBX-216 at 1-2; Gottesman Stmt., RBX-4C at 6-8; RBPX-101; Gottesman Tr., 1714-1716, 1842; Kleid Tr., 853; Falkinham, Tr. 1015, 1020).

RBX-216 is from BTG and RBX-216 is titled "Glossary of Certain Technical Terms."

108. With respect to the relationship to human growth hormones of

the initial expressed Met-hGH polypeptide would not have the tertiary structure shown in RBPX-100. It would look something like RBPX-101. The cystines would be reduced. There would be no disulfide bridges and it would be an insoluble aggregate within inclusion bodies in the bacteria. After processing outside the bacteria, one would arrive at a biologically active hormone which was properly folded and had the cystines oxidized and disulfide bonds formed but, the tertiary structure of this form of Met-hGH is different in some significant way from that of hGH because the active form of Met-hGH is antigenic in humans and hGH is not (Gottesman, RBX-4, Q. 21).

109. The met-hGH expressed in E. coli is materially different from the final purified hGH. The expressed Met-hGH is insoluble, reduced and inactive and is present bound to E. coli proteins within inclusion bodies consisting of aggregates of met-hGH and other E. coli proteins. In contrast, the final purified hGH does not have the terminal methionine. It is one hundred and ninety-one amino acids. It is soluble. It is not reduced. It includes the disulfide bridges and it has a tertiary structure which permits it to be active biologically (Gottesman, RBX-4, Q. 24).

110. In BTG's process

111.

112.

113. Plasmid is in fact different from biologically active, properly folded, soluble, non-reduced human growth hormone.

The DNA plasmid bears no resemblance to, and is purified away from, the final product, viz. biologically active human growth hormone which is a protein (Gottesman, RBX-4, QQ. 31, 32).

114.

What is expressed in the BTG process is not a properly folded or active form of either hGH or Met-hGH. The form of Met-hGH expressed is improperly folded, biologically inactive, insoluble and reduced. The inactive form of Met-hGH is not isolated and purified by BTG (Gottesman, RBX-4, Q. 39).

115. RBPX-102 are photographs which show the bacterium Escherichia coli. There are two panels. The upper photograph shows the normal or wild type (wt)

bacterium and the lower photograph shows a mutant form (rpoH) of the E. coli bacterium. In the mutant, as shown by arrows, there is extensive formation of inclusion bodies. Those inclusion bodies contain insoluble bacterial proteins, are not present in the normal bacterium and are found only in these special mutant bacteria. Inclusion bodies form not only in the mutant bacterium, but also in E. coli whenever there is overproduction of a particular protein

116.

the final product is authentic human growth hormone which is present in a biologically active form including the disulfide bridges and the appropriate tertiary structure (Gottesman, RBX-4 at 9-10; RBX-101 at 114-124, 148-149; RBX-104; RBX-106; Gottesman, Tr. at 2144-2149, 2728 to 2735).

117.

RBX-110; Gottesman, Tr. at 1983-1986, 2145-2148, 2159-2161, 2742-2752).

118.

119. When Gottesman was asked if when human growth hormone is expressed within the human body, it is expressed with a leader sequence, he answered [t]hat's correct, sir" (Tr. at 1954). He stated that what's expressed within the cell has a leader sequence and he agreed that what is expressed is a different product than what is outside the cell (Tr. at 1955, 56). He also agreed that after the translation step, the cell in the human body is producing something that will ultimately become the product human growth hormone although the polypeptide is not even finished while it still has the leader on it (Tr. at 1956-57). When the expression product is still within the cell, the expression product being that which will become human growth hormone is not bioactive (Tr. at 1857). Gottesman would characterize such expression product as an "unfinished human growth hormone and inactive" (Tr. at 1857-58).

120. In the human body, while the leader sequence is making its way out of the cell, the leader sequence is cleaved off (Tr. at 1962). Gottesman agreed that a portion of the human growth hormone will be outside the cell before the translation is complete (Tr. at 1962, 63).

121. Gottesman agreed that in the human body, while the translation is

complete within the cell, half the expression product is in the cell and half is outside the cell and although the material is not folded properly, when the tail end of the polypeptide finally gets outside the cell and folds then one has human growth hormone as shown in RBPX-100 (Tr. at 1963).

122. The primary sequence of amino acids is part of what determines the characteristics of a protein. Also the way it folds or is modified contributes to the characteristics of a protein. The folding however is actually determined by the particular amino acid sequence of the polypeptide. Amino acids in proteins are strung together in different orders to produce all of the known proteins. It is the particular sequence in which the amino acids are strung together which defines the identify of a particular protein although there are a few proteins with odd amino acids.

123. The particular sequence of amino acids in a protein defines the identity and the chemical characteristics of that protein (Gottesman, Tr. at 2323-24).

124. It is the binding of the growth hormone to the receptor (the ashtrays in RBPX-100) that allows the growth hormone to be active and that transmits the signal into the cell. When a 192 polypeptide, the methionine being the 192nd amino acid, is folded, the polypeptide will bind to the receptor and it will have biological activity and it will promote linear growth in humans. It is also antigenic which suggests maybe it is not folded quite properly in every respect (Gottesman, Tr. at 2325-26).

125. The tertiary structure in RBPX-100 refers to the three dimensional structure (Gottesman, Tr. at 2327).

126. The information for folding is in the primary sequence of the polypeptide represented by the unfolded RBPX-101 (Gottesman, Tr. at 2327).

127. A properly folded, soluble, disulfide linked protein molecule of one hundred and ninety-one amino acids with biological activity does not exist inside a human cell nor does it exist inside a bacterial cell (Gottesman, Tr. at 2330).

128. When Falkinham was asked whether he understands a chemical definition of human growth hormone, he answers "[a] protein composed of 191 amino acids, which is produced by the pituitary of humans, if we are referring to human growth hormone" (Falkinham, Tr. at 999).

129. As to the formation of disulfide bonds in human growth hormone, there is one particular amino acid in proteins called cysteine which has the property of being able to get oxidized. When two molecules of cysteine get oxidized, the two cysteines come together to form what is called a disulfide covalent bond which in effect causes a cross-linking of the chains of the protein (Kleid, Tr. at 364-65).

130. The amino acid cystine has two sulfurs hooked together in a covalent sulphur-sulphur bond. The amino acid cysteine is in the reduced form and the two sulphurs are not covalently bonded (Kleid, Tr. at 365).

131. Human growth hormone has its own three-dimensional globular structure which is attributed, in part, to the formation of a chemical bond referred to as a disulfide bond between specific amino acid residues (cysteine residues) within the chain of human growth hormone amino acids. Those disulfide bonds cause the protein to fold back on itself and, consequently, give the molecule a shape - - its three-dimensional structure. When human growth hormone is in a three-dimensional configuration, it is biologically active (Kleid, CX-231 at 3).

132. The disulfide bond in human growth hormone can only form outside of

E. coli because E. coli is a reducing atmosphere and that atmosphere prevents the formation of disulfide bonds. Such disulfide bonds are really essential to fold the molecule properly so it will be active (Gottesman, Tr. at 1718).

133. In the case of human growth hormone, the activity of the hormone is dependent upon it being folded in the proper configuration, and its activity as a pharmaceutical agent would need the disulfide bond (Kleid, Tr. at 486-87).

134. When Gottesman reads the phrase "method of producing human growth hormone" in claim 2 of the '980 patent he reads the term "human growth hormone" in said phrase as something outside the cell. Also with respect to the claimed phrase "expressed human growth hormone" in the last line of claim 2, he agrees that said phrase purports to refer to the product at a stage before isolation while the product is still inside the cell, and hence according to Gottesman's definition of the term "human growth hormone," the use of the term "human growth hormone" in the last line of claim 2 is a misnomer because human growth hormone has not been expressed inside a bacteria (Gottesman, Tr. at 2332-33).

135. The word "culturing" in connection with bacterial transformants means that cells are able to grow, divide, propagate and form colonies. Transformants means that the cells carry a plasmid and the plasmid has the gene that encodes the human growth hormone (Gottesman, Tr. at 1812).

136. Gottesman assumes from a reading of claim 2 of the '980 patent and the phrase "unaccompanied by the leader sequence of human growth hormone or other extraneous protein bound thereto" that the protein is not bound to the gene but is bound to the product. Gottesman testified that one "could have the human growth hormone as contaminated with other proteins. And sure enough

that's why you go through all these purification steps" (Gottesman, Tr. at 1836, 1837, 2345, 2346).

137. The '908 specification at col. 3, lines 8-12 states that "[a]t the same time it would be desirable to express such products unaccompanied by conjugate protein, the necessity of whose expression requires diversion of resources within the organism better committed to construction of the intended product." Gottesman understands that sentence as indicating that it would be desirable to express the product unaccompanied by the superfluous protein, such as in the '619 patent, comprised of the "beta galac" protein (Gottesman, Tr. at 1982).

138. There is expert testimony that the word "expression" is an open ended term. It simply means that DNA codons are transcribed and translated into amino acids and that biologically human growth hormone must be expressed as met-human growth hormone because the latter is the only form in which any protein could be expressed in E. coli. All proteins are initiated with methionine (the amino encoded by the ATG codon) and hence one expects its presence unless removed. BTG's Marian Gorecki described the human protein, apolipoprotein E (ApoE) - - when part of Met-ApoE - - as being "expressed" and in this context Gorecki described human growth hormone - - when part of met-human growth hormone - - as being expressed (Falkinham, CX-7 at 31, 32).

139. All mammalian proteins expressed in bacteria will begin with a met. Processing will always be necessary, to one degree or another, after expression in a bacterial cell to get the expressed product in active, usable form.

140.

I. The '980 Patent

141. Claim 2 of the '980 patent reads as follows:

> A method for producing human growth hormone which method comprises culturing bacterial transformants containing recombinant plasmids which will, in a transformant bacterium, express a gene for human growth hormone or other extraneous protein bound thereto, and isolating and purifying said expressed human hormone.

(CX-4, col. 13, ll. 3-10).

142. The '980 patent, entitled "Microbial Expression Of A Gene For Human Growth Hormone" was issued on July 22, 1986 to David V. Goeddel and Herbert L. Heyneker, and is assigned on its face to Genentech.

143. Under the subheading "Genetic Expression" (CX-4, col. 1, line 9) in connection with "Background of the Invention" the '980 patent discloses:

> The DNA (deoxyribonucleic acid) of which genes are made comprises both protein-encoding or "structural" genes and control regions that mediate the expression of their information through provision of sites for RNA polymerase binding, information for ribosomal biding sites, etc. Encoded protein is "expressed" from its corresponding DNA by a multistep process within an organism by which:
>
> 1. The enzyme RNA polymerase is activated in the control region (hereafter the "promoter") and travels along the structural gene, transcribing its encoded information into messenger ribonucleic acid (mRNA) until

transcription of translatable mRNA is ended at one or more "stop" codons.

2. The mRNA message is translated at the ribosomes into a protein for whose amino acid sequence the gene encodes, beginning at a translation "start" signal, most commonly ATG (which is transcribed "AUG" and translated" [f-methionine").

(CX-4, col. 1, lines 10-28).

144. Under the subheading "Human Growth Hormone" (col. 3, line 43), the inventors on the '980 patent disclose:

> In summary, a need has existed for new methods of producing HGH and other polypeptide products in quantity, and that need has been particularly acute in the case of polypeptides too large to admit of organic synthesis or convenient synthesis of genes from which the peptide could be expressed. Expression of mammalian hormones from mRNA transcripts has offered the promise of side-stepping difficulties that attend the synthetic approach, but until the present has permitted only microbial production of bio-inactive conjugates from which the desired hormone could not practicably be cleaved.

(CX-4, col. 3, lines 56-67).

145. The '980 patent is based on application Ser. No. 356,564 filed March 9, 1982 which is a division of Ser. No. 55,126 filed July 5, 1979.

146. In the '980 patent there is a heading titled "Construction and Expression of a Cloning Vehicle for Human Growth Hormone" followed by a subheading "1. Cloning the Hae III fragment of the mRNA transcript (FIGS. 3 and 4) (CX-4, col. 8, lines 4-8). Said subheading section gets the so-called cDNA, puts it into plasmid PBR-322 (col. 8, line 29) and makes copies of it so there is a bunch of them which can be used. Confirmation of the codons for amino acids 24-191 of the human growth hormone were confirmed (CX-4, col. 8, lines 10 to 68, col. 9, lines 1-35).

147. The '980 patent has a section titled "2. Construction and Cloning of the Synthetic Gene Fragments (FIGS. 1 and 2)" (CX-4, col. 9, lines 35-68,

col. 10, lines 1-20). This section as indicated in its text tells one how to put together the smaller fragment that is going to encode amino acids 1 to 23 of human growth hormone. The section which title has the word "cloning" also reflects the fact that one does not want to make only one small fragment but rather makes a supply of the small fragments to work with.

148. The '980 patent has a section titled "3. Construction of Plasmid for the Bacterial Expression of HGH (FIG. 5)" (CX-4, col. 10, lines 21-22). In this section it is reported that with the synthetic fragment in pHFH3 and the mRNA transcript in pHGH31 from the earlier sections, a replicable plasmid containing both fragments was constructed using the expression plasmid pGH6. The paragraph that starts at col. 11, line 6 of the section refers to checking out the plasmids to make certain one has the right ones. Thus the "bacterial transformants containing recombinant bacterium" recited in claim 2 are found in said section which commences at col. 10, line 21. That section recites that "[h]uman growth hormone expressed by the transformants was easily detected by direct radioimmunoassay performed on serial dilutions of lysed cell supernatants using the Phadebas HGH PRIST kit (Pharmacia)" (col. 11, lines 27-31) which complainant represents satisfies the following recitation in claim 2: "express a gene for human growth hormone unaccompanied by the leader sequence of human growth hormone or other extraneous protein bound thereto" (Tr at 2714-15). Complainant also takes the position that the recitation at col. 11, lines 27-31 states that the cells have been lyced or made to open up but one does not have full purification yet and the whole concept of recovery or isolation and purification also recited in claim 2 involves multi-step possibilities; that one first gets a rough purification or a rough recovery by getting rid of some of the garbage that one does not want

and obtains something more concentrated and at any stage one can speak of having recovered or purified the recited "[h]uman growth hormone" (col. 11, line 28) to some degree and one can carry the purification of recovery to whatever ultimate stage one wants; that at this stage of having lyced those cells (col. 11, line 29), in a sense some recovery, isolation, purification has taken place although not to the final point that one wants for pharmaceutical purposes but sufficient at least to run the direct radioimmunoassay. According to complainant the final isolation and purification is at col. 12 starting at line 53 (Tr. at 2715-16).

149. Illustrative conditions for the "culturing" recited in claim 2 are at col. 12, lines 30-46 of the '908 patent. Thus the '980 specification states in this regard that:

> transformant E. coli cultures may be grown up in aqueous media in a steel or other fermentation vessel conventionally aerated and agitated, in aqueous media . . . supplied with appropriate nutriments such as carbohydrate or glycerol, nitrogen sources such as ammonium sulfate, potassium sources such as potassium phosphate, trace elements, magnesium sulfate and the like.

(CX-4, col. 12, lines 31-39).

150. The '980 patent discloses chemically synthesizing a 24 codon DNA fragment corresponding to the 23 codons missing from the hGH fragment plus an ATG start codon, and fused that fragment to the cDNA fragment (CX-4, col. 9, line 36 to col. 10, line 19, col. 10, line 44 to col. 11, line 5). The resulting "semi-synthetic" gene construct was then inserted into a bacterial plasmid adjacent to a bacterial control region, minus its own start codon (CX-4, col. 11, lines 11-12). The plasmid was then expressed in a bacterial cell under the control of a homologous control region (Kleid, CX-5 at 16, CX-4, col. 11, lines 28-31. There is testimony that the expressed material was then

purified by standard techniques which work was immediately published in Nature (Kleid, CX-5 at 16, 18; CPX 6-70). There is also expert testimony that "Seeburg et al, working in the laboratory of Howard Goodman, who for years worked with growth hormone-encoding DNA sequences, were unable to produce functional rat growth hormone, because they had no way to get rid of the inactivating leader encoding sequence which accompanied their cDNA." The problem addressed and solved in the '832/'980 patents is to remove the unwanted leader from a cDNA and then to replace the terminal portion of the protein coding sequence (Chamberlin, CX-21 at 8, 10).

151. Nature (CPX 6-70) is cited on page 4 of the '619 patent (CX-2) and its complete citation is Vol. 281 at 545-548 (1979). It stated in part:

> DNA coding for human growth hormone was constructed by using chemically synthesized DNA in conjunction with enzymatically prepared cDNA. This 'hybrid' gene was expressed in Escherichia coli under the control of the lac promoter. A polypeptide was produced having the size and immunological properties characteristic of mature human growth hormone.
>
> HUMAN GROWTH HORMONE (HGH) is a protein of 191 amino acids which is synthesized in the anterior lobe of the pituitary. Growth in hypopituitary dwarfs, whose small stature is due to a defficiency of HGH, can be restored during childhood by administration of this hormone. In addition, HGH may prove effective in the treatment of a variety of aliments, including bone fractures, skin burns and bleeding ulcers. As growth hormone is species specific, human cadavers have been the only source of HGH.
>
> * * *
>
> **Conclusion**
>
> Using a novel combination of chemically synthesized DNA and cDNA, a recombinant E. coli strain has been constructed which produces HGH in large amounts. This is the first time that a human polypeptide has been directly expressed-in E. coli in a non-precursor form. The hybrid DNA cloning techniques described as a route to the cloning and expression of HGH coding sequences in E. coli are generally applicable to other polypeptide which are

> synthesized initially as inactive precursors and later processed, or for which full length cDNA transcripts are unavailable.

(Id. at 545, 548).

152. Encoded protein is "expressed" from its corresponding DNA by a multistep process within an organism by which:

> 1. The enzyme RNA polymerase is activitated in the control region (the "promoter") and travels along the structural gene, transcribing its encoded information into messenger ribonucleic acid (mRNA) until transcription of translatable mRNA is ended at one or more "stop" codons.
>
> 2. The mRNA message is transloaded at the ribosomes into a protein for whose amino acid sequence the genencodes, beginning at a translation "start" signal, most commonly ATG (which is transcribed "AUG" and translated" f-methionine").

(CX-4, col. 2, lines 15-28).

153. Aside from the use of cloning vehicles to increase the supply of genes of replication, there have been attempts, prior to the July 5, 1979 initial filing date of the '980 patent, some successful, to actually express proteins for which the genes code. In the first such instance a gene for the brain hormone somatostation under the influence of the lac promoter was expressed in E. Coli bacteria. K. Itakure et al. Science 198, 1056 (1977). More recently, the A and B chains of human insulin were expressed in the same fashion and combined to form the hormone. D. V. Goeddel et al., Proc. Nat'l Acad. Sci. USA 76, 106 (1979). In each case the genes were constructed in their entirety by synthesis. In each case, proteolytic enzymes within the cell would apparently degrade the desired product, necessitating its production in conjugated form, i.e., in tandem with another protein which protected it by compartmentalization and which could be extracellulary cleaved away to yield the product intended (CX-4, col. 2, lines 50-67).

154. The '980 patent discloses under the heading "Summary of the Invention" that:

> The present invention provides methods and means for expressing quasi-synthetic genes wherein reverse transcription provides a substantial portion, preferably a majority, of the coding sequence without labonous resort to entirely synthetic construction, while synthesis of the remainder of the coding sequence affords a completed gene capable of expressing the desired polypeptide unaccompanied by bio-inactivant leader sequences or other extraneous protein. Alternatively, the synthetic remainder may yield a proteolysis-resistant conjugate so engineered as to permit extra-cellular cleavage of extraneous protein, yielding the bioactive form. The invention accordingly makes available method and means for microbial production of numerous materials hitherto produced only in limited quantity by costly extraction from tissue, and still others previously incapable of industrial manufacture. In its most preferred embodiment the invention represents the first occasion in which a medically significant polypeptide hormone human growth hormones) has been bacterially expressed while avoiding both intracellular proteolysis and the necessity of compartmentalizing the bioactive form in extraneous protein pending extracellular cleavage. Microbial sources for human growth hormone made available by the invention offer, for the first time ample supplies of the hormone for treatment of hypopituitary dwarfism, together with other applications heretofore beyond the capacity of tissue-derived hormone sources, including diffuse gastric bleading, pseudarthrosis, burn therapy, wound healing, dystrophy and bone knitting.

(CX-4, col. 4, lines 3-33).

155. Under the heading "Detailed Description of the Invention," the '980 patent discloses that:

> The general approach of the invention involves the combination in a single cloning vehicle of plural gene fragments which in combination code for expression of the desired product. Of these, at least one is a cDNA fragment derived by reverse transcription from mRNA isolated from tissue, as by the method of A. Ullrich et al, Science 196, 1313 91977). The cDNA provides a substantial portion, and preferably at least a majority, of the codons for the desired product, while remaining portions of the gene are supplied synthetically. The synthetic and mRNA transcript fragments are cloned

separately to provide ample quantities for use in the later combination step.

A variety of considerations influence distribution of codons for the end product as between synthetic and cDNA, most particular the DNA sequence of complementary DNA determined as by the method of Maxam and gilbert, Proc. Nat'l Acad. Sci. USA 74, 560 (1977). Complementary DNA obtained by reverse transcription will invariably contain codons for at least a carboxy terminal portion of the desired product, as well as other codons for untranslated mRNA downstream from the translation stop signal(s) adjacent the carboxyl terminus. The presence of DNA for untranslated RNA is largely irrelevant, although unduly lengthy sequences of that kind may be removed, as by restriction enzyme cleavage, to conserve cellular resources employed in replicating and expressing the DNA for the intended product. In particular cases, the cDNA will contain codons for the entire amino acid sequence desired, as well as extraneous codons upstream from the amino terminus of the intended product. For example, many if not all polypeptide hormones are expressed in precursor form with leader or signal sequences of protein involved, e.g., in transport to the cellular membrane. In expression from eukaryotic cells, these sequences are enzymatically removed, such that the hormone enters the piroplasmic spaced in its free, bioactive form. However, microbial cells cannot be relied upon to perform that function, and it is accordingly desirable to remove sequences from the mRNA transcript. In the course of that removal process the translation start signal is also lost, and almost invariably some codons for the intended product will be removed as well. The synthetic component of the quasi-synthetic gene product of the invention returns these latter codons, as well as supplying anew a translation start signal where the vehicle into which the hybrid gene will ultimately be deployed itself lacks a properly positioned start.

(CX-4, col. 4, lines 67-68, col. 5, lines 1 to 50).

156. Under the subheading "Detailed Description of the Invention" the invention discloses that:

Applications will appear in which it is desirable to express not only the amino acid sequence of the intended product, but also a measure of extraneous but specifically engineered protein. Four such applications may be mentioned by way of example. First, the quasi-synthetic gene may represent a hapten or other immunological determinant upon which immunogenicity is conferred by

> conjugation to additional protein, such that vaccines are produced. See generally, G.B. patent specification 2 008 123A. Again, it may be desirable for biosafety reasons to express the intended product as a conjugate with other, bio-inactivating protein so designed as to permit extracellular cleavage to yield the active form. Third, applications will be presented in which transport signal polypeptides will precede the desired product, to permit production of the same by excretion through the cell membrane, so long as the signal peptide can then be cleaved. Finally, extraneous conjugate designed to permit specific cleavage extracelullarly may be employed to compartmentalize intended products otherwise susceptible to degradation by proteases endogenous to the microbial host. At least in the latter three applications, the synthetic adaptor molecular employed to complete the coding sequence of the mRNA transcript can additionally incorporate codons for amino acid sequences specifically cleavable, as by enzymatic action. For example, trypsin or [sic] will cleave specifically at arg-arg or lys-lys, etc. See GB No. 2 008 123A, supra.

(CX-4, col. 7, lines 3-32).

157. According to the '980 patent, the patent's broadest aspect the invention admits of manifold applications, each having in common these attributes:

> a mRNA transcript is employed which codes for a substantial portion of the intended polypeptide's amino acid sequence but which, if expressed alone, would produce a different polypeptide either smaller or larger than the intended product;
>
> protein-encoding codons for amino acid sequences other than those contained in the intended product, if any, are removed;
>
> organic synthesis yields fragment(s) coding for the remainder of the desired sequence; and
>
> the mRNA transcript and synthetic fragment(s) are combined and disposed in a promoter-containing cloning vehicle for replication and expression of either the intended product absent extraneous conjugated protein, or intended product conjugated to but specifically cleavable from extraneous protein. (Emphasis added)

The expression product will in every case commence with the amino acid coded

for by the translation start signal (in the case of ATG, f-methionine). One can expect this to be removed intracelluarly, or in any event to leave the bioactivity of the ultimate product essentially unaffected (CX-4, col. 7, lines 32 to 57). Because the specifications of the '980 and '832 patents are substantially identical, the above occurs also in the '832 patent at col. 7, lines 48-64).

158. The inventors disclose with respect to isolation of the expression product:

> Upon completion of fermentation the bacterial suspension is centrifuged or the cellular solids otherwise collected from the broth and then lysed by physical or chemical means. Cellular debris is removed from supernatant and soluble growth hormone isolated and purified.
>
> Human growth hormone may be purified from bacterial extracts using one or a combination of (1) polyethyleneimine fractionation; (2) gel filbration chromatography on Sephacryl S-200; 93) ion exchange chromatography on Biorex-70 resin or CM Sephadex; (4) ammonium sulphate and/or pH fractionation; and (5) affinity chrommatographhy using antibody resins prepared from anti-HGH IgG isolated from immunosensitized animals or hybridomas; and desorbed under acid or slightly denaturing conditions.

(CX-4, col. 12, lines 48 to 62).

159. Complainant's Dr. Bennett testified that "the techniques of polyethyleneimmine fractionation, Sephacryl S-200 chromatography, Biorex-70 chromatography, CM Sephadex chromatography, pH fractionation, and immunoaffinity chromatography employing anti-human growth hormone antibodies, combined with the knowledge possessed by one of ordinary skill in protein purification prior to July 5, 1979, would have permitted such a person to prepare from E. coli strain x1776/pGH107 human growth hormone of any desired purity" (Bennett, CX-19 at 2).

160. Goeddel and Heyneker reported the bacterial expression of hGH in

Nature Vol. 281, pp. 544 to 548 (October 18, 1979) (CPX-6-70, RBX-118) and their article describes using the techniques outlined in the patent to purify hGH. Thus Fig. 5 (CPX-6-70) describes the partial purification of the bacterially expressed hGH using some of the purification steps describe in the '832/'980 patents, the authors determining that the hGH was purified to approximately 25%. Complainant's scientists further purified the expressed hGH. Thus using techniques mentioned in the '832/'980 patents, the expressed hGH was later purified to "near homogeneity" and used for in vivo analyses of weight gain and tibia growth in rats. This purification and the assay results were reported in Nature Vol. 293, pp. 408 to 411 (October 1, 1981) by Olsen et al. (CX-105) (Kleid, CX-5 at 18).

161. Nature (CPX-770, RBX-118, at 548), with reference to its Fig. 5, states:

> Fig. 5 Identification of HGH produced in bacteria by SDS-polyacrylamide gel electrophoresis. a. Protein patterns of crude extracts and partially purified HGH stained with Coomassie brilliant blue. Slot 1 contains 0.5 ug of pituitary HGH standard (Kabi), slot 2 contains a cell lysate of RV308/pHGH107, slot 3 contains a cell lysate of RV308/pBR322, slot 4 contains partially purified HGH isolated from $_{x}$1776/pHGH107. The samples were separated on a 15% polyacrylamide slab gel using the buffer system of Maizel with the addition of 6 M urea. Crude lysates were prepared by growing cells in LB with 5 ug ml^{-1} tetracycline followed by lysis in 2% SDS, 1% B-mercaptoethanol. The lysates were precipitated with 10 volumes of cold acetone and the pellets were redissolved in SDS sample buffer for use in gel electrophoresis. The partially purified HGH was prepared from a stationary phase culture of $_{x}$1776/pHGH107. Cells were collected and resuspended in 1/50 of their original volume in 30 mM potassium phosphate (pH 7.0) containing 0.05 M NaCl and lysed by sonication. Polyethylenimine (Miles, Polymin-P) was added to 0.2%. After centrifugation for 1 h at 100.000g. ammonium sulphate was added to the supernatant to 60% saturation. The ammonium sulphate pellet was dissolved in 2 ml 10 mmM potassium phosphate (pH 7.0), 0.5 M NaCl and chromatographed on a Sephacryl S-200 column (2.0 x 50 cm) equilibrated in the same buffer. The

radioimmune active peak (assayed with a Pharmacia Phadebus HGH kit) was pooled, the protein concentrated by ammonium sulphate precipitation, the pellet redissolved in 1/10 volume of buffer, and the solution dialysed against 10 mM potassium phosphate (pH 7.0), 0.5 M NaCL. Preipitated material was removed by centrifugation resulting in a HGH preparation of approximately 25% purity. b. Autoradiograms of ^{23}S-labelled extracts of RV308/pHGH107. Slot 1 contains a total lysate of RV308/pHGH107 labelled with $H_2{}^{33}SO4$. Slot 2 contains an ^{33}S-labelled extract of RV308/pHGH107 precipitated with a-HGH antiserum. The major (top) band co- migrates with unlabelled HGH standard (not shown). Cultures (1 ml) of RV308/pHGH107 were grown to A 550=1 in low sulphur medium containing 0.2 mCi ml-$^{1}H2\ ^{33}SO_4$, chased with 10 mMgSO_4 for 5 min, collected and lysed using Triton X-100 and lysozyme. Following DNase and RNAse treatment, the lysate was mixed with a 10-fold excess of unlabelled RV308/pBR322 extract and diluted 1:1 into Triton immuno-precipitation buffer (0.15 Mm NaCl, 1% Triton X-100, 0.05 M Tris-HCl pH 7.5). Twenty ul of a-HGH antiserum (Kabi) was added per ml of original culture and the reaction was incubated for 12 h at 4#C. The mixture was centrifuged and the supernatant incubated for 2h with foraidehyde fixed Staphylococcus cells, filtered on 0.45-um Nucleopore polycarbonate filters, washed with Triton immunoprecipitation buffer and extracted with SDS sample buffer. The samples were run on a 15% slab gel-containing urea and SDS as described above. [Footnotes omitted]

162. BTG's scientist, Dr. Panet testified:

Q Are you saying that in [1977] people had available to them a wider variety of purification tools that they would understand how to apply to a particular purification problem?

A People had pretty much the same methodologies, broad methodologies, as they have today, they had 20 years ago. The same columns, we have now better machines. We can apply pressure to get the purification faster. But we basically use the same principles that we have used when I was undergraduate.

Q And so when presented with a particular task of purifying a particular protein, you would have to look at the basic principles and tune them to apply to your particular problem?

A Pretty much, and you can derive the same purification procedure by two independent methods. Which would give you have the same product ultimately.

Q In other words, to use an American phrase, there's more than one way to skin a cat?

A Yes. And more than that. There is nothing novel in the way in which you arrive to the final pure protein. I mean, it's -- I would put it within the scope of technology. You could take the technology. You don't need to be an inventor to get a protein pure.

Q Okay. I mean at BTG a skilled technician would do a purification, would devise a purification scheme and that would apply to human growth hormone as well as other products?

A This would apply to proteins in general.

Q Including human growth hormone?

A As I said, proteins in general.

Q Okay.

A If you ask about human growth hormone protein, yes.

(Panet, CPX-28 at 151-153) (Emphasis added).

163. BTG's Panet, in a declaration, stated "[R]ecovery of polypeptide was well known to those skilled in the art, e.g., Lehninger (Chapter 7)." (RBX-20).

164. BTG scientist, Dr. Abraham Havron, stated:

A With the methods available at that time, the material which is the subject of this patent could have been purified.

Q Could have been?

A Could have been purified.

Q Yes.

(Havron, CPX-23 at 43).

165. Complainant's Kleid testified that basically by using the purification techniques described in the '980/'832 patents, one could take several approaches to purify the expression product described in said patents to any degree of purity (Kleid, CX-5 at 17). When Kleid was asked whether that statement referred "to human growth hormone present in inclusion bodies", he testified "No, That refers to the experiments in the '832 and '980 patents"

Tr. at 887).

166. Complainant's Chamberlin testified:

Q Do you know whether there is a standard procedure applicable to the recovery of proteins from inclusion -- E-coli inclusion bodies?

A I haven't any idea whether there's a standard procedure. However, there are certainly accepted procedures that work often.

Q Do you know whether those procedures work for human growth hormone?

A I haven't any idea.

JUDGE LUCKERN: Now, you're talking about standard procedures. Can you illustrate?

THE WITNESS: Well, standard procedures for the purification of a protein or, in this case, the disruption of an insoluble protein have been established for some time.

In the case of disrupting the inclusion bodies, for example, normally what you'd do would be to treat with something that would denature the protein.

So, that could be a denaturing agent such as guanidinian hydrochloride or urea, sometimes high salts will do it. What those do then is to disperse the protein and allow you to carry out traditional methods of biochemical fractionation which normally require a soluble protein.

There is a certain art involved in the purification of a protein. And there are journals that publish hundreds of articles every month on subtle modifications of techniques.

So, those really -- those types of procedures would fall under what I would call, as somebody who's an enzymologist, prior art. There certainly is nothing impossible about purifying a protein from an inclusion body.

JUDGE LUCKERN: Thank you. Go ahead, Mr. White.

BY MR. WHITE:

Q You referred in your discussion of solubilizing the inclusion bodies to substances such as guanidinian

hydrochloride and urea, correct?

A Yes, I did.

Q Will those substances denature a protein?

A Yes, they will.

Q Will a denatured protein be biologically active?

A Certainly, after it's been renatured.

Q Well, prior to it being renatured, will a denatured protein be biologically active?

A No.

(Tr. at 641-642).

167. In a paper titled "Human pitiutary growth hormone: Restoration of full biological activity by noncovalent interaction of two fragments of the hormone" in Proc. Natl. Acad. Sci. USA Vol. 73, No.5, pp. 1476-1479 (May 1976) Choh Hao Li and Thomas A. Bewley disclose how a reduced human growth hormone molecule is readily oxidied to the active hormone (CPX-6-122). The Li and Bewley research describing the formation of hGH disulfide bonds was originally reported in a paper entitled "Human Pituitary Growth Hormone XXII: The Reduction and Reoxidation of the Hormone", published in the Archives of Biochemistry and Biophysics, Vol. 138, pages 338-346 (1970) (CX-233) (Kleid, CX-5 at 5).

J. The '832 Patent

168. Claim 1 of the '832 patent reads as follows:

> 1. In the method of constructing a replicable cloning vehicle capable, in a microbial organism, of expressing a particular polypeptide of known amino acid sequence wherein a gene coding for the polypeptide is inserted into a cloning vehicle and placed under the control of an expression promoter,
>
> the improvement which comprises:
>
> (a) obtaining by reverse transcription from

messenger RNA a first gene fragment for an expression product other than said polypeptide, which fragment comprises at least a portion of the coding sequence for said polypeptide;

(b) where the first fragment comprises protein-encoding codons for amino acid sequences other than those contained in said polypeptide, eliminating the same while retaining at least a substantial portion of said coding sequence, the resulting fragment nevertheless coding for an expression product other than said polypeptide;

the product of step (a) or, where required, step (b) being a fragment encoding less than all of the amino acid sequence of said polypeptide;

(c) providing by organic synthesis one or more synthetic non-reverse transcript-gene fragments encoding the remainder of the amino acid sequence of said polypeptide, at least one of said fragments coding for the amino-terminal portion of the polypeptide; and

(d) deploying the synthetic gene fragment(s) of step (c) and that produced in step (a) or (b), as the case may be, in a replicable cloning vehicle in proper reading phase relative to one another and under the control of an expression promoter;

whereby a replicable cloning vehicle capable of expressing the amino acid sequence of said polypeptide is formed.

(CX-2, col. 13, lines 7 to 42).

169. The '832 patent, entitled "Method of Constructing a Replicable Cloning Vehicle Having Quasi-Synthetic Genes" was issued on August 3, 1982 to David V. Goeddel and Herbert L. Heyneker, and is assigned on its face to Genentech (CX-3).

170. The '832 patent is based on the applications Ser. No. 55,126, filed July 5, 1979. Because the '980 patent is based on application Ser. No. 356,564 which is a division of Ser. No. 55,126 the specifications of the '980 and '832 patents are identical in all substantive aspects (CX-3, CX-4).

171. With respect to claim 1 of the '832 patent step (a) is always

required and cannot be omitted. Step (b) may or may not be utilized in the practice of claim 1. Steps (c) and (d) are always utilized in the practice of claim 1 (Tr. at 2761).

172. Instead of BTG actually making the first gene fragment recited in claim 1 of the '832 patent BTG took a donation of it from Goodman at the University of California. Thus according to complainant the actual step of getting messenger RNA and carrying out the reverse transcription called for in step (a) was performed by Goodman of the University of California. BTG's position is that BTG obtained a full length cDNA from the University of California and did not obtain by reverse transcription anything and also that what vBTG obtained was not a gene fragment as that term is used in step(a) because it encoded theentire DNA and included the leader sequence (Tr. at 2764, 2765, 2766, 2767).

173. Referring to the section of the patent titled "1. Cloning the Hae III fragment of the mRNA transcript (FIGS 3 and 4)" (CX-3, col. 8, line 20-22) the first portion of the section thru line 35 corresponds to step (a) of claim 1 of the '832 patent and the cutting step (b) of claim 1 of the '832 patent starts at line 36. The step (b) product is missing the first 23 amino acids.

174. The subsection of the '832 patent titled "2. Construction and Cloning of the Synthetic Gene Fragment (FIGS. 1 and 2)" relates to step (c) of claim 1 of the '832 patent (CX-3, col. 9, lines 48-50).

175. In the subsection identified in the preceding finding, the '832 patent states that "[t]he methionine codon at the left end provides a site for initiation of translation" (col. 9, lines 66, 67). The '832 patent,as to Figures 1 and 2, states:

> FIG. 1 depicts the synthetic scheme for construction of a gene fragment coding for the first 24 amino acids of human growth hormone, together with the start signal ATG and linkers used in cloning. The arrows in the coding or upper strands ("U") and in the complementary or lower strands ("L) indicate the oligonucleotides joined to form the depicted fragment:
>
> FIG. 2 depicts joinder of the "U" and "L" oligonucleotides to form the gene fragment of FIG. 1 and its insertion in a plasmid cloning vehicle:

(CX-3, col. 4, lines 38 to 48).

176. Step (d) of claim 1 of the '832 patent is carried out in the section of the patent titled "3. Construction of Plasmid For The Bacterial Expression of HGH (Fig. 5)" (CX-3, col. 10, lines 33-34).

177. Claim 1 of the '832 patent does not recite any step of expression. Rather a replicable cloning vehicle capable of expressing the amino acid sequence of a polypeptide is obtained (CX-3).

178. According to BTG's Gottesman, step (a) of claim 1 of the '832 patent and the recitation "(a) obtaining by reverse transcription from messenger RNA a first gene fragment" the term "first gene fragment" comes from isolating messenger RNA from pituitary and treating messenger RNA with an enzyme called reverse transcriptase which copies the RNA into a DNA from which is called cDNA. Also according to Gottesman the '832 patent discloses a gene for human growth hormone that has one part made up of cDNA and the rest of it made up of organically synthesized DNA (Tr. at 1908, 1909, 2017).

179. it does use that plasmid to express a "form of Met-hGH which is not in the sense of known being present out in nature" but it is a polypeptide of known amino acid sequence. It has 192 amino acids and those are known (Gottesman, Tr. at 1908).

180. The '832 patent disclosed under the subheading "Detailed

Description of the Invention" (CX-3, col. 4, lines 65-66):

> "The general approach of the invention involves the combination in a single cloning vehicle of plural gene fragments which in combination code for expression of the desired product. Of these, at least one is a cDNA fragment derived by reverse transcription from mRNA isolated from tissue, as by the method of A. Ullrich et al., Science 196, 1313 (1977). The cDNA provides a substantial portion, and preferably at least a majority, of the codons for the desired product, while remaining portions of the gene are supplied synthetically. The synthetic and mRNA transcript fragments are cloned separately to provide ample quantities for use in the later combination step" [Col. 4, lines 67-68, col. 5, lines 1-11].

181. With respect to the phrase in claim 1 "(d) deploying the synthetic gene fragment(s) of step (c) and that produced in step (a) or (b), as the case may be, in a replicable cloning vehicle in proper reading phase relative to one another" Gottesman testified as to the term "reading phase" that when one puts together the cDNA and the fragments, it is important that they not be out of step with each other so that the codons are read in groups of three and they are read in the same groups of three throughout the entire clone gene; and that for example if one put in an extra nucleotide by mistake, one would throw the whole frame off and one would read by the right groups of three up to that insert and then after that it would all be garbage and so it is important that they be aligned properly so that the whole polypeptide can be expressed. He agreed that if they are not aligned properly, one would likely to produce a nonsense polypeptide (Tr. at 2025).

182. The last phrase of claim 1 of the '832 patent reads "under the control of an expression promoter." Gottesman when asked whether the usage of the word "control" in said phrase is simply talking about the action of the promoter in causing the expression or the transcription to be carried out, testified that "I think that's probably what the inventors mean here" (Tr. at

1873). He also testified that there is no question that

183. Broadly, speaking there were two approaches to making a gene using biologically-derived material. One approach is to isolate DNA directly from the nucleus of a cell; this is referred to as genomic DNA. The other approach is to prepare "complementary" or "copy" DNA -- "cDNA," if one wished to use the genomic approach one first isolate human cells. One then isolates the DNA and cut it up into fragments which are of a size suitable for cloning. Finally, one can select the gene of choice from among the cloned fragments. A primary difficulty here is that there are thousands of genes in each human chromosome, so getting the gene one wants is extraordinarily difficult. Because many of the genes of interest are not expected to provide the microbial host cell with any competitive advantage, one would be left with the task of finding the right sequence out of thousands. One wants to insert only the structural gene that encodes the protein one wished to express. When one isolates genomic DNA one generally brings along a lot of extra DNA. Thus the fragment containing the structural gene may contain sequences upstream of the structural gene, for example the mammalian control region. In addition, within many mammalian genes, there are "intervening sequence" -- or "introns." These are sequences which do not encode protein and which in fact interrupt the correct protein sequence. The mammalian control region however will not be recognized by the microbial cellular machinery. Also the presence of DNA in between a microbial control region and the structural gene could result in synthesis of an inactive fusion protein or could put the mammalian gene out of reading phase. In addition human cells have machinery which removes these intron sequences. Microbial cells lack this machinery and have no need for it

because microbial genes lack introns. As a result, introns in microbial cells prevent the protein from being made correctly. Also there is at least one other problem. Many human genes encode an additional amino acid sequence, the so-called "leader sequence," that is not part of the mature, functional protein (Falkinham, CX-7, QQ. 50, 51, 52, 53, 54, 55, 56).

184. The mammalian cell has cellular machinery which removes the leader sequence during its concomitant synthesis and secretion. Though microbial cells also secrete certain proteins and these proteins contain the microbial equivalent of leader sequences, the *E. coli* machinery cannot recognize the mammalian leader sequences and remove them. Consequently, the mammalian protein is produced with an amino-terminal leader sequence. Such leader sequence-containing proteins are nonfunctional (Falkinham, CX-7, Q. 57).

185. The material cDNA is made from mRNA (Falkinham, CX-7, Q. 58).

186. The mRNA is a faithful copy of one of the two strands of the DNA of a particular gene. It is made by the cell during the process of transcription, and it forms the template for the synthesis of protein during the process called translation. It is isolated from cells producing a lot of the proteins of interest. For example, if one wanted to isolate mRNA for the hGH protein, the pituitary gland would be the source. An enzyme called "reverse transcriptase" is used to make a copy of the mRNA. This enzyme uses the mRNA to direct the synthesis of the DNA (Falkinham, CX-7, QQ. 59, 60).

187. The cDNA approach solves the problem of introns. The mRNA template used for the cDNA copy does not include the introns -- they are not there to be copied. It is an edited version of the mRNA which is used to make a cDNA molecule. Because of this, the intron problem is solved by the cDNA approach. The leader sequence problem, however, is not solved by the cDNA approach.

Leader sequences are not removed by this process (Falkinham, CX-7, Q. 61).

188. In the method of Goeddel and Heyneker in the '832 patent for creating a particular DNA sequence, they began by preparing cDNA from mRNA which was highly enriched for hGH mRNA. The mixture of cDNA was treated with a protein called a "restriction endonuclease," an enzyme which cuts DNA at a specific sequence. This allowed Goeddel and Heyneker to remove the leader sequence and to clone a fragment of the hGH gene which lacked the leader sequence. It also lacked a portion of the human growth hormone gene. The portion missing was the beginning of the gene -- the amino-terminus. The next step was to chemically synthesize a piece of DNA coding for the missing portion of the gene. That was possible because the length of the sequence missing was not prohibitively long. These two fragments, the cDNA and the chemically synthesized sequences, were combined to produce a semi-synthetic gene encoding the desired protein which in turn produced hGH (Falkinham, CX-7, QQ. 64, 66, 67). In the late 1970's and even today there were, and are, no restriction endomideases or other enzymes or chemicals available to cut DNA anywhere at will (Falkinham, CX-7 at 25).

189. The '832 patent draws a clear distinction between a structural gene which is that portion that can encode the 191 amino acids and the word "gene" which is a broader term. Thus the '832 patent states that the "DNA (deoxyribonucleic acid) of which genes are made comprises both protein - encoding or 'structural' genes and control regions that mediate the expression of their information through provision of sites for RNA polymerase binding, information for ribosonal binding sites etc." (CX-3, col. 1, lines 9-12).

190. Step (a) of claim 1 of the '832 patent recites obtaining by reverse transcription from messenger RNA a fragment. The first gene fragment of step

(a) may be larger or smaller than the DNA sequence coding for the 191 amino acid sequence that is common to all forms of human growth hormone (Chamberlin, Tr. at 664-665; CX-3, claim 1).

191.

192.

193. Gottesman testified:

193(a). It is clear that scientists would regard

still being an "mRNA transcript fragment." The '832 patent uses "mRNA transcript" to refer to the clones as well as the original transcripts. In col. 5, lines 8-11, the patent says "the synthetic and mRNA transcript fragments are cloned separately

to provide ample quantities for use in the later combination step." Then, at col. 9, lines 58-62, the specification says that the "mRNA transcript [i.e., the clone] and synthetic fragment would ultimately be joined" [Emphasis added].

the cloning step does not create any changes of substance in the function or result inteded by the claimed invention, or the way in which the function and result are carried out. In addition

is completely consistent with the alternatives set out in the '832 specification and in claim 1. In col. 5, lines 28-31, the '832 specification says as follows "[i]n particular cases, the cDNA will contain codons for the entire amino acid sequence desired, as well as extraneous codons upstream from the amino terminus of the intended product." Claim 1 accommodates use of such a "full length" cDNA gene fragment by saying that the "first gene fragment ... comprises at least a portion of the coding sequence for said polypeptide" [Emphasis added] (col. 13, lines 15-18). The words "at least a portion" imply that the whole coding sequence may appear in the first fragment. Section "(b)" of the claim then deals with this "full length" alternative by saying that "where" the first fragment has excess codons, these are removed to leave (col. 13, lines 27-28) "a fragment encoding less than all of the amino acid sequence of said polypeptide."

K. Goodman.358

194. Goodman et al,., U.S. Patent No. 4,363,877 (Goodman patent) was issued from an application filed April 19, 1978 as a continuation-in-part of an earlier application filed September 23, 1977 (RBX-119).

195. The Goodman patent was issued from an application filed April 19, 1978 as a continuation-in-part of an earlier application filed September 23, 1977 (RBX-119).

196. The Goodman patent names as one of the inventors Peter H. Seeburg (RBX-119).

197. Example 5 (including Table 5) of the Goodman patent at column 23-26 discloses a cDNA encoding amino acids 24-191 of human growth hormone which was obtained by reverse transcription of messenger RNA. HaeIII digestion was also involved (RBX-119; Gottesman, Tr. at 1966).

198. Example 7 of the Goodman patent at column 28 discloses a cDNA encoding the entire gene sequence for human growth hormone, i.e. amino acids 1-191 which was obtained by reverse transcription. (RBX-119; Gottesman, Tr. at 1966). The cDNA of Goodman's examples 6 and 7 also included the DNA sequence encoding "a 26 amino acid sequence found in the growth hormone precursor protein prior to secretion", i.e., the leader sequence (RBX-119; CX-337 (Chamberlin) at 3).

199. Goodman et al. prior to July 5, 1979 published a paper (Goodman paper) on which Peter H. Seeburg and Axel Ullrich are coauthors (RBX-120 at

179; Chamberlin, Tr. at 664-665).

200. Figure 1 of the Goodman paper discloses a cDNA encoding amino acids 24-191 of human growth hormone which was obtained by reverse transcription of messenger RNA (RBX-120 at 180; Chamberlin, Tr. at 664-665; Gottesman, Tr. at 1966).

201. On July 6, 1979, the Nature magazine received a manuscript on which David V. Goeddel, Herbert L. Heyneker, and Peter H. Seeburg are coauthors (RBX-118 at 548).

202. The manuscript received by Nature on July 6, 1979 was accepted for publication on August 16, 1979 and was published on October 18, 1979 (Goeddel paper) (RBX-118 at 548).

203. Figure 3 of the Goeddel paper discloses the amino acid and mRNA sequence of hGH as determined by DNA sequencing of phGH 131 (RBX-118 at 546).

204. Figure 3 of the Goeddel paper is identical to Figure 3 of the '832 Patent (RBX-118 at 546; CX-3 at 3 or 5).

205. Figure 5 of the '832 patent is substantially identical to Figure 1 of the Goodman paper and to Table 5 of the Goodman Patent (Gottesman, RBX-4 at 44; RBX-119; RBX-120; Chamberlin, Tr., 668-669, 681). Table 5 of the Goodman patent is DNA, while Fig. 1 of the Goodman paper is mRNA (the two sequences are otherwise identical). Fig. 3 of the '832 patent is not identical to either Fig. 1 of the Goodman paper or Table 5 of the Goodman patent. Thus Fig. 3 of the '832 patent differs from both Goodman references in that it shows a 5' G which the Goodman references lack, and the 3' untranslated regions are different in several respects in the region from nucleotides 593-598 (CX-3; RBX-119; and RBX-120).

206. The '832 patent does not refer to the Goodman cDNA. The '832

reexamination file history refers to the Goodman patent as follows, where applicants requested reexamination in view of several references, including the Goodman patent: "[T]he record is not clear that the examiner [in the original prosecution] made a patentability determination based on that portion of the Backman reference quoted above. This portion appears to be closer prior art than the cited Itakura (Science, 1977) reference which is directed to the organic synthesis of gene sequences, separately, or considered in view of the Goodman patent (4,363,877), the Seeburg article (Nature, 1978) or the Villa-Komaroff article (PNAS, 1978) all of which are directed to cDNA techniques." The PTO examiner said the following, in response to the reexamination request: "No substantial new question of patentability is raised by the ... prior art cited ... for the reasons set forth below. * * * Some motivation, absent here, must exist for organic chemically synthesizing part of a whole structural gene so as to supply the missing sequences of that gene. Only hindsight can provide that subtle, although essential, knowledge and hindsight is abhorrent to patentable judgments. Gore v. Garlock 220 USPQ at 312-13. Accordingly, no substantial new question of patentability is raised in view of the Backman et al. reference alone or in combination with known prior art documents" (CPX-9).

207. The hGH cDNA described in the '832/'980 patents and in the Goeddel Nature article was synthesized by Goeddel using RNA obtained apparently from Peter Seeberg. Complainant's notebook #85, page 73, shows an experiment for constructing hGH cDNA (CX236, dated 4/19/79). This experiment led to the synthesis of the hGH cDNA used by Genentech and published by Goeddel and Heyneker in their 1979 Nature article. Goeddel notes on page 74 that the RNA he used for this experiment came from P. Seeburg (CX236, dated 4/20/79).

Complainant's hGH cDNA was synthesized at complainant (Kleid, CX-231 at 6).

208. The Goodman paper discloses step (a) of claim 1 of the '832 patent. (Chamberlin, Tr. at 664; RBX-120).

209. The Goodman group did not fail to achieve step (a) of claim 1 of the '832 patent (Chamberlin, Tr. sy 682-683; Gottesman, Tr. at 2049-2051).

210. It was quite common at the time '832 patent was filed and in fact it still is common to obtain an incomplete cDNA, i.e. a gene fragment by reverse transcription from messenger RNA (Chamberlin, Tr. at 683; Gottesman, Tr. at 2060-2061).

211. The Goeddel paper states that the techniques described are generally applicable to polypeptides that are initially synthesized as inactive precursors and later processed or for which full length cDNA transcripts are unavailable (RBX-118 at 548; Chamberlin, Tr. at 699; Gottesman, Tr. at 2060-2061).

212. According to complainant's Chamberlin, it might take three years to obtain cDNA encoding amino acids 24-191 of human growth hormone (Chamberlin, Tr. at 697).

213. Complainant's Chamberlin has no knowledge when, where or by whom step (a) of claim 1 of the '832 patent was carried out (Chamberlin, Tr. at 658, 698).

214. The Goeddel paper indicates that the RNA used was prepared by Peter H. Seeburg while he was at the University of California (Gottesman, RBX-4C at 45).

215. Peter Seeburg and Axel Ullrich left the University of California and were employed by complainant (Kleid, Tr. at 916).

216. The cDNA encoding the fragment of human growth hormone gene

disclosed in the '832 patent was prepared by Goeddel and P. Seeburg eluted the cDNA from a gel (Kleid, CX-231 at 6; Kleid, Tr. at 927; CX-236 at 73-74).

217. Kleid testified:

Turn to 6648 of RBX-140, Doctor.

* * *

BY MR. WHITE:

Q Dr. Kleid, would you read the line that appears under the -- about two-third approximately down the page under this tabulated data, first reading it aloud in Exhibit CX-236C?

* * *

A All right. "Reaction mixtures made up at 0 degrees C; reactions run at 42 degrees C for 15 minutes."

JUDGE LUCKERN: This isn't your writing is it? This is the writing of somebody else; correct?

THE WITNESS: Dr. Goeddel. I witnessed --

JUDGE LUCKERN: You witnessed it. I see there.

So all right. Go ahead.

BY MR. WHITE:

Q This is Dr. Goeddel's handwriting; correct?

A I believe so. Yes.

Q Well, you witnessed the page. Do you know? All of the pages in this notebook you witnessed. Do you have any doubt that this is his handwriting?

A Not as I sit here today. No.

Q Now, you indicated that -- it was read, "Reaction mixtures made up at 0 degrees C." Is that correct?

A That's what I read. Yes.

Q Now, would you look really carefully at these two different versions of this page and tell me if one of them doesn't read U, degree symbol C, and the other one has been altered to read zero degrees C?

A I don't see that. That's no alterations at all. I mean, this has been xeroxed 20 million times. When I did this affidavit I happened to have the original notebook in my hands because it was produced -- it was used in my deposition last week with Eli Lilly. I spent last week being deposed for a week.

(Kleid, Tr. at 930 to 932).

L. Importation

218.

219.

220.

221. A purpose of research using human growth hormone supplied by BTG was to explore the structure-function relationship of human growth hormone molecule may be responsible for its various biological activities CPX-35 at 104; RBX-84; RBX-11 at 1).

222. has been interested in the structure-function of human

growth hormone for 28 years. The research performed using human growth hormone supplied by BTG was in furtherance of his long-standing intellectual interest CPX-35 at 103-104; RBX-84).

223. research used human growth hormone supplied by BTG and the materials supplied by BTG were neither sold to any party nor distributed outside of

224. never received any instructions from BTG regarding his research, and BTG did not try to direct experiments in any way. Dep., CPX-35 at 106; RBX-84).

225. is a basic scientist conducting basic research in the search for new knowledge , CPX-35 at 41; RBX-84).

226. has never had any contact with regarding the patentability of any of his research findings Dep., CPX-35 at 124-125).

227. After completing the experiment, was a coauthor of a scientific paper published in

228. The paper in the preceding finding is an accurate summary of experiments conducted at (CPX-35-27).

229. has finished his experiment, has no on-going activity and is in the process of retiring (CPX-35-26; RBX-11).

230. Although does not have the capability to take a new drug to market, he agrees that the work he did in conjunction with the Israel Binational Science Foundation grant has potential commercial uses. While does not know BTG's commercial intent relating to his studies with the BTG hGH CPX-35 at 85-86, 98); a grant application which filed

with the acknowledged the potential commercial benefits flowing from his studies. In particular, in the grant application at page 9, wrote as follows:

> D. Significance:
>
> Knowledge obtained in this work will provide a more precise understanding of the relationships between the structure of hGH and its diverse biological actions.
>
> The ultimate goal of such work is to gain the information needed to design mutant growth hormone molecules with altered potencies or lacking certain underiable activities, such as the diabetogenic property. The virtue of such a goal is clear. For example, biosynthetic hGH has been approved for human uses and is available in abundant supply. Yet the immense therapeutic potential of the protein anabolic property of this hormone will never be realized, unless a way if found to eliminate its diabetogenic activity.
>
> CPX-35 at 96-97; CPX-35-28 at 9).

231. In deposition on December 2, 1993, stated:

> MR. CLARK: Page 9, paragraph D [see preceding finding]. He just read that into the record. I said, do you agree with what's written here, and he said, I wrote it. That's where we left off.
>
> BY MR. CLARK, CONTINUING:
>
> Q So you were stating here, weren't you, Doctor that in your view there was a potentially therapeutically beneficial result from carrying out the work described in this proposal?
>
> What I was describing was that this work might ultimately contribute to such a therapeutically advantageous thing in the sense that we would be providing basic knowledge that anyone could use.
>
> Q Anyone, including BTG?
>
> A Yes.
>
> Q Do you still believe that in may be possible to design mutant growth hormone molecules which lack undesirable activities such as diabetogenic properties?
>
> A My belief now is no. That is my belief.

Q Did you believe it was possible when you wrote this grant application we're looking at, Exhibit 28, in 1989?

A Yes.

(CPX-35 at 97, 98).

232. A third party, who peer-reviewed application for a National Science Foundation grant covering the same studies with the BTG hGH, acknowledged the potential commercial applications of the results obtained from the work:

> Better understanding of human action mechanisms would no doubt lead to clinical benefits as well as providing insights for understanding actions of other hormones.

(CPX-35 at 99-102; CPX-35-30).

233. In deposition on December 2, 1993, stated:

Q ... Now, I'll hand you again Exhibit 30 [see preceding finding] and ask you to read the sentence beginning with the word better.

A "Better understanding growth hormone action mechanisms would no doubt lead to clinical benefits as well as providing insights for understanding actions of other hormones."

Q Who is the author of that sentence? Can you tell from the page?

A Grants are reviewed, peer reviewed anonymously.

Q When you say peer reviewed, that indicates what about the author of this sentence?

A That indicates that that person would be -- should be -- should be reasonably conversive with the field.

Q Do you agree with that last sentence from this anonymous reviewer that you just read into the record?

MS. SORINI: Now, you mean? In this time period?

BY MR. CLARK, CONTINUING:

Q Well, let me break it up. Did you agree at the time you received that review with that sentence?

A Yes.

Q Do you agree with it now?

A It's a very general statement and better understanding of any biological mechanism is going to possibly lead to clinical benefits. So in terms of the very general statement, yes, I agree with it.

(CPX-35 at 101, 102).

234.

work involved a study of the mutant

forms of hGH to CPX-35 at 14-18).

235. on December 2, 1993, stated:

Q Let me refer back for a moment to a statement in a exhibit that has already been marked. I want to refer you to a [Exh. 2]

* * *

BY MR. CLARK, CONTINUING:

Q Please turn to page 4253. And we have already read the last sentence of that page into the record. I'd like to read it again or have someone else read it.

* * *

BY MR. CLARK, CONTINUING:

Q "An understanding of the mechanisms at the molecular level will enhance the understanding of various biological activities observed and permit tailor-made forms of growth hormones to target only the actions desired, with the potential of reducing or eliminating biological activities that are deemed undesirable."

Now, that sentence that I just read refers, does it not, to potential drugs?

A It could.

Q Returning now to Exhibit 7, the question I asked before in a slightly different way in light of the sentence I just read from Exhibit 2, did you believe that assays such as those you proposed carrying out that hGH mutants could have had practical implications in the development of drugs?

MS. SORINI: For human use?

MR. CLARK: For human use.

THE WITNESS: Depending on the outcome, they could.

* * *

MS. SORINI: Before you start, I had an opportunity to speak with Doctor about the last answer to the question that -- the last question and, yes, he wanted to give a clarification as far as what practical aspects his research could be used at. Would you like to say what we were talking about, or --

THE WITNESS: What I would like to say is that my research is basic research. I do not have the capability to take findings that are made in my laboratory and bring them to some practical fruition like the development of a drug. I have never done that, I never will do it. That's not what I am. I'm a basic scientist searching for new knowledge.

* * *

Q Yes, I understand. Let me clarify the previous question as well. When I was asking whether the results could have practical implications in drug development, I didn't mean practical implications for drug development by you in you lab, I meant generally.

A Yes.

* * *

Q For example, let me follow -- state a follow-up question just a make that clear. Could those results possibly have been useful in the hands of a drug development company to develop drugs, the results that we were discussing before the break; that is, the carrying out of the --

A Yes, they could. If they are published in the literature, they are available for anyone to take and do anything with them -- what they wish, yes.

Q How could -- let me make -- I'd like to refer to a document when I ask this question. I believe we were on Exhibit 7.

* * *

BY MR. CLARK, CONTINUING:

Q Referring now to Exhibit 7, which is a letter dated September 1, 1988 from you to Doctor Gertler which you have already identified, that letter suggests carrying out on the hGH mutants assays for the growth-promoting diabetogenic and insulin-like properties of the molecules, correct?

A It does.

Q My question is, could the results of those assays on the hGH mutants have provided to a drug development company information which would have been useful to that company in drug development?

A Yes.

(CPX-35 at 39 to 43).

236. BTG supplied human growth hormone under the terms of an agreement entitled "AGREEMENT RELATING TO THE TRANSFER OF BIOLOGICAL MATERIAL". The agreement contains the following provisions: inter alia:

1. BTG will provide samples of hGH mutants (hereinafter, "biological materials") produced by BTG to to investigate their effect on different physiological activities.

2. acknowledges and agrees that BTG shall retain all rights, title and interest in and to such biological materials and to research results derived free using such biological materials. The biological materials will not be used in research that is subject to consulting or licensing obligations to another entity.

3. further agrees that such biological materials will be used only for research within and will not be given to any other person or entity without BTG's prior written consent.

4. additionally agrees that she [sic] will advise BTG in writing concerning the results of research which utilizes the biological materials; will provide to BTG copies of all scientific manuscripts which concern such research prior to submitting such manuscripts for publication; will not disclose information to third parties and will not submit manuscripts for publication without BTG's written consent, such consent will not be withheld unreasonably; and will include as co-authors on such manuscripts the appropriate BTG scientists. BTG will review manuscripts within three (3) months or receipt. If BTG can do so without compromising its present or potential patent rights, BTG will waive all or a portion of this three month period.

(SX-22 at 2).

237. BTG imported human growth hormone for the purpose of conducting feasibility studies in conjunction with Enzytech, Inc.'s (Enzytech) Prolease delivery system (Fass, RBX-2 at 25).

238. Experiments at Enzytech were conducted in animals to determine whether daily authentic human growth hormone injections could be replaced with weekly or bi-weekly injections (Fass, RBX-2 at 25-26).

239. Experiments with Enzytech's Prolease delivery system did not demonstrate feasibility. As a result, BTG terminated this research effort and its relationship with Enzytech (Fass, RBX-2 at 26).

240. BTG-Israel manufactured human growth hormone used by DuPont in the human clinical studies (Fass, RBX-2 at 4). BTG shipped human growth hormone in bulk form from Israel to ABI in Canada for filing. (Fass , RBX-2 at 4). ABI then shipped the product from Canada to DuPont in the United States for use in clinical trials. DuPont completed the human clinical studies (Fass, RBX-2 at 4).

241. BTG has no commercially labelled inventory of human growth hormone product in the United States (Fass, RBX-2 at 24).

242. There were shipments of BTG's human growth hormone products to be used for feasibility studies in connection with efforts of a company called Affinity to develop a suppository delivery system. This effort was terminated (Fass, RBX-2 at 24).

243. All inventory of BTG's human growth hormone product in the U.S. is earmarked for use only in clinical trials and is so labelled (Fass, RBX-2 at 26).

M. Domestic Industry

244. PROTROPIN (called SOMMATREM for injection) is one Genentech brand of hGH. It is currently sold commercially in the U.S. market as a treatment for human growth hormone deficiency in children. PROTROPIN received FDA approval for commercial sales for this indication on October 17, 1985. Complainant began selling PROTROPIN in the U.S. market for this indication shortly thereafter in 1985 (Matlock, CX-8 at 6).

245. Complainant has manufactured PROTROPIN on a commercial scale at its facilities in South San Francisco since 1985 for the treatment of human growth hormone deficiency in children (Whiting, CX-38 at 2).

246. The shelf life of PROTROPIN is approximately 18 months (Whiting, CX-38 at 5).

247. In July 1993, complainant submitted to the FDA its NDA for the use of NUTROPIN, another Genentech brand of hGH, to treat short stature associated with chronic renal insufficiency (Matlock, RBPX-18 at 76).

248. NUTROPIN is also the subject of an NDA pending before the FDA for growth hormone deficiency in children (Matlock, CX-8 at 7).

249. Complainant has manufactured NUTROPIN for Investigational New Drug ("IND") approval and NDA clinical studies since 1985, using the same facilities in South San Francisco as used for the production of PROTROPIN (Whiting, CX-38 at 2).

250. Complainant performs all steps in the manufacturing process of PROTROPIN and NUTROPIN in the United States at its facilities in South San Francisco, except that it subcontracts some filling of PROTROPIN to

(Whiting, CX-38 at 4-5, 7).

251. The majority of all materials used in the process for production of

PROTROPIN and NUTROPIN is produced in the United States (Whiting, CX-38 at 5, 7).

252. Through 1992, complainant has invested over in production facilities for its human growth hormone products. This figure does not reflect the cost of complainant's R&D laboratories, administrative support offices, or the like (Lavigne CX-3C) at 4; (Whiting) CX-38 at 3. Of the approximately is devoted to the production of PROTROPIN; the to the production of NUTROPIN (Whiting, CX-38 at 3; RBX-23 at GITC 012 6882).

253. Except with respect to the recovery step where there are columns specific to either NUTROPIN or PROTROPIN, production facilities for PROTROPIN and NUTROPIN are essentially the same (Whiting, RBPX-22 at 66; CX-38 at 8).

254. Equipment used in the production of PROTROPIN and NUTROPIN is essentially interchangeable (except for the equipment used in the recovery stage and other minor steps) (Whiting, RBPX-22 at 75).

255. Employees associated with production of PROTROPIN and NUTROPIN are essentially interchangeable (Whiting, RBPX-22 at 75).

256. Complainant is revising its production process for NUTROPIN at a cost of This revision will require expenditures of on capital equipment and manufacturing re-configuration, and for producing FDA process qualification lots; the revision will be completed in December 1993. The revision will permit complainant to process more NUTROPIN at one time during the recovery stage of processing (Whiting, CX-38 at 8).

257. Complainant's manufacturing facilities currently devoted to the production of PROTROPIN encompass square feet and the facilities

devoted to the production of NUTROPIN encompass approximately square feet (Whiting, CX-38 at 5, 7).

258. The major types of equipment used in the production of hGH products include fermentors, extensive piping, computer control systems, sterile filling equipment, and lyopholizers (Whiting, CX-38 at 3).

259. Genentech employs approximately full-time equivalent people ("FTE") in the production of PROTROPIN and approximately FTEs in the production of NUTROPIN (Whiting, CX-38 at 5, 7).

260. In 1991, complainant produced approximately kgs. of PROTROPIN, almost all for commercial sale. In 1992, Genentech produced approximately kgs. of PROTROPIN, almost all for commercial sale (Whiting, CX-38 at 5).

261. From its inception in 1976 through 1992, complainant has invested over $1.3 billion in R&D. (The $1.3 billion does not include complainant's costs of commercial production facilities, annual adjustments for complainant's cost of capital, nor the cost of acquiring technology rights from R&D limited partnerships for complainant's products) (Lavigne, CX-30 at 2; RBX-23 at GITC 012 6883).

262. Approximately of the total development spending in 1976 through 1992 was attributable to projects that were terminated because they were judged to be . In addition, a substantial portion of the research spending during this period was terminated before development, and the final outcome of

(Lavigne, CX-30 at 2).

263. Pioneering biotechnology companies and their investors face a magnitude of scientific and commercial risks stemming from the uncertainty of obtaining FDA approval for new drugs and the uncertainty as to whether a drug

can be manufactured on a commercial scale (Lavigne, CX-30 at 3).

264. In developing its human growth hormone products, PROTROPIN and NUTROPIN, complainant expended approximately on research and development costs through December 31, 1992 (including depreciation of R&D facilities and the acquisition costs of technology rights from complainant's R&D limited partnership). This amount does not fully reflect complainant's actual R&D costs: for example, the does not include an allocation of the costs of (Lavigne, CX-30 at 3; RBX-25 at GITC 012 6878; Niall CX-34 Niall at 8).

265. In complainant's PROTROPIN production process, complainant began with mRNA from the pituitary gland and using reverse transcriptase, complaintant produced hGH cDNA. The cDNA for hGH included the hGH structural gene as well as the leader sequence. This cDNA was cut with a restriction enzyme ,leaving a fragment encoding hGH amino acids 24 to 191. The fragment was cloned into a transfer vector, and to this vector, was added organically synthesized DNA encoding amino-terminal amino acids 1-23 and an ATG start codon tomproduce a semi-synthetic gene for hGH with an amino-terminal Met. The semisynthetic gene was inserted into a microbial expression plasmid under the control of a control region and the plasmid was introduced (or inserted) into microbial E. coli cells where hGH with an amino-termninal Met was produced. The hGH with an amino-terminal Met is isolated and purified from the cells (Falkinham, CX-7 at 54).

266. In complainant's NUTROPIN production process complainant began with its semi-synthetic hGH gene. Complainant then removed the start codon and joined to the beginning of the gene a DNA fragment (including the start codon) of a bacterial protein provides a natural selective

cleavage site at the junction with hGH which site is cut by an E. coli cell protease. This gene is inserted into an exprfession plasmid unbder the control of a control region and hGH with an amino-terminal is expressed in E. coli. The E. coli cell precisely removes the STII protein by cutting at the selective cleavage site adjacent hGH. The end result is the production of met-free hGH (Falkinham, CX-7 at 60).

267. With respect to claim 1 of the '832 patent in the PROTROPIN process, complainant's plasmid cloning vehicle with its semi-synthetic gene, expresses the polypeptide hGH with an amino-terminal methionine. The cloning vehicle is replicable and works in E. coli, a bacterial cell. Complainant's semi-syntheic gene is then inserted into its plasmid and the semi-synthetic gene is placed under the control of the expression promoter. Complainant's initial cDNA fragment encodes hGH accompanied by its leader sequence, a product other than hGH, either with or without an amino-terminal Met. The cDNA fragment encodes hGH, which is also the hGH portion of Met-hGH. Thereafter cutting the initial cDNA fragment eliminates codons for other thanb hGH, leaving a fragment encoding a sybstantual portion (but not the entirety) of either hGH with an amino-terminal met or met-free hGH, Comnplainant's synthetic DNA fragment is an organmically synthesized fragment encoding the amino-terminal remainder of both hGH with an amino terminal Met and met-free hGH. Complainant's combined fragments are inserted into its plasmid in proper reading phase such that hGHJ with an amino-terminal methionine and Met-free hGH is expressed under the control of the expression promoter (Falkinham, CX-7 at 58-59).

268. Complainant produces hGH with an amino-terminal methionine. Complainant cultures microbial E. coli transformants which contain a plasmid

expressing hGH. The expressed hGH is unaccompanied by leader sequence or other extraneous protein bound thereto because Met is not a protein; it's a single amino acid (Falkinham, CX-7, Q. 122).

269. With respect to complainant's PROTROPIN process and claim 2 of the '980 patent, complainant produces hGH with an amino-terminal methionine. Complainant's recombinant plasmid containing semi-synthetic DNA that encodes hGH is expressed in E. coli, the transformant bacterium. The expressed hGH is unaccompanied by the leader sequence or any other extraneous protein bound thereto. The expressed hGH is then isolated and purified, still with an amino-terminal Met (Falkinham, CX-7 at 56).

270. With respect to claim 2 of the '980 patent and the NUTROPIN process, complainant's plasmid containing semi-synthetic DNA that encodes hGH is expressed in E coli, the transformant bacterium. The expressed hGH is unaccompanied by the leader sequence of human ghrowth hormone or any other extraneous protein bound thereto in that the expressed

is not an unremovableamino acid sequence, but rather is an additional sequence that is cleaved by the bacterial cell to yield hGH. The expressed hGH is then isolated and purified (Falkinham, CX-7 at 62).

N. FDA Approval

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273. On December 1, 1987, DuPont filed a New Drug Application (NDA) with the United States Food and Drug Administration (FDA) for the indication of growth hormone deficiency in children (CPX-131 at 3; Fass, RBX-2 at 3).

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275. The original Investigational New Drug (IND) and NDA were transferred to BTG form DuPont in April 1992 (Fass, RBX-2 at 4).

276. BTG's NDA is pending before the FDA (Fass, RBX-2 at 5).

277. Eli Lilly Co.'s (Lilly) human growth hormone product HUMATROPE has received Orphan Drug status, which entitles Lilly to a seven year period of exclusivity during which time no other authentic human growth hormone for growth hormone deficiency may be marketed in the United States (Fass, RBX-2 at 5). The seven year period of exclusivity for HUMATROPE is due to expire on March 6, 1994 (Fass, RBX-2 at 5; Matlock, CX-8 at 8).

278. Approval of BTG's NDA has been blocked by HUMATROPE'S Orphan Drug status (Fass, RBX-2 at 5).

279. Without FDA approval of the NDA, BTG is proscribed from selling, marketing, advertising, promoting or in any way commercializing its human growth hormone in the United States (RBX-5 at 4).

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295(a). Serono has a new drug application (NDA) pending with FDA for its hGH product which was submitted in March, April 1993. Serono did submit a NDA for growth hormone in '87 or '88 but approval was denied because of the orphan drug law.

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297. Prior to joining BTG, Fass was a general manager of Wampole Laboratories division of Carter-Wallace for three years and prior to that was a pharmaceuticals marketing and diagnostics general management executive with Pfizer Pharmaceuticals for eleven years (Fass, RBX-2 at 1-2).

298. BTG's Senior vice president Stephen Simes was responsible for sales and marketing of products when he was the President and Chief Executive Officer for Gynex Pharmaceutical, Inc. (Gynex) prior to its merger with BTG, and had experience in development of marketing and sales when he was a product manager with Searle Pharmaceuticals (Simes, CPX-30 at 5, 10-11).

299. BTG's Senior vice president of finance, Mathew Pazaryna, came to BTG from a twenty-five year career at Johnson & Johnson (Fass, Tr. at 1602).

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315. The shelf-life for BIOTROPIN in Europe is 18 months.

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Q. Relative Competitive Positions

322. Complainant's expert witness, Dr. Henry G. Grabowski, was qualified at the hearing as an expert with respect to "economic issues including effects of competition and determinants of research and development expenditures" (Tr. at 2092-93).

323. Bonnie S. Matlock, complainant's associate director of endocrinology and immunology products, was qualified as an expert in business decision making, projections, effects, and terms of competition in the U.S. growth hormone market (Matlock, CX-8 at 1; Tr. at 1316-17, 1331).

324. BTG's expert witness, Dr. Susan Henley Manning, was qualified as an expert in industrial organizations, which is the study of the functioning of markets; specifically the structure and behavior of firms, including market strategies and internal organization, market competition, market entry and price theory (Tr. at 1677).

325. Complainant has a share of the United States market for hGH products (Matlock, Tr. at 1334).

326. In 1992 complainant sold dollars of hGH. In 1992 complainant sold dollars of hGH. Complainant's sales of hGH in 1993 are expected to total dollars (Matlock, CX-8 at 23).

327. Matlock testified that the major elements of competition in the U.S. market for sales of hGH for growth hormone deficiency include price, service, the reputation of the manufacturer, product attributes (including administrative procedures), and distribution (Matlock, CX-8 at 18).

328. Matlock testified that a course of treatment for growth hormone deficiency on hGH costs the average patient approximately $18,000 per year in ex factory prices, i.e. the price charged to the distributor (Matlock, CX-8 at 18).

329. Matlock testified that for managed care providers price is the major determinant in deciding which hGH is selected; that for other direct purchasers, such as pharmacies, value-added services are more important than price, although Matlock testified that if price deviates sufficiently between hGH products that are otherwise competitive (or even different in competitive attributes), price becomes the determining factor; and that if the price deviation is sufficiently large, even a product that is not otherwise competitive in terms of value-added services and the like will have the advantage (Matlock, CX-8 at 18).

330. Matlock testified at the hearing that the most important customer group is pediatric endocrinologists (Matlock, Tr. at 1305).

331. RBX-35C is a report entitled "U.S. Growth Hormone Market: Competition 1994 -- Conjoint Analysis" (Conjoint Analysis), which was prepared

for complainant by (RBX-35; Matlock, RBPX-18 at 225).

332. In the "Conjoint Analysis," pediatric endocrinologists ranked the major elements of competition in the U.S. human growth hormone market, in order of importance, to be: (1) service; (2) price; (3) reputation of the manufacturer; (4) product attributes; and (5) distribution (Matlock, RBPX-18 at 225, 255, 259; RBX-79; RBX-35 at GITC 005 3023).

333. Grabowski testified that although value-added services are an important competitive factor for some segments of the market, service is secondary to price in the of the market, citing as least likely to buy on the basis of services and most likely to buy on the basis of price (Grabowski, CX-6 at 8; Grabowski, CX-230 at 4).

334. Pediatric endocrinologists are the group in the market that are most service and product-attribute oriented (Grabowski, CX-230 at 73).

335. Complainant's manager of managed care department, Kenneth P. Gross, testified that he believed that even if an HMO knew that a supplier would not be in the market in the future, there would still be "a certain price point" at which the HMO would buy because of the price "for four or five months" and would deal with the issue of locating another supplier "in four or five months" (Gross, RBPX-7 at 5, 81).

336. Gross believes that such a point "would be somewhere from a price reduction" (Gross, RBPX-7 at 81).

337. Grabowski testified that there is a preference among pediatric endocrinologists to avoid switching brands during the course of treatment. (Grabowski, Tr. at 2095).

338. The government sector of the U.S. hGH market, consisting of Medicaid and the military, is believed to be very price sensitive (Grabowski,

CX-6 at 8).

339. In 1993 complainant expended over dollars, and has expended over dollars to date, on its National Cooperative Growth Study (NCGS). The NCGS collects information on the use and results of complainant's hGH PROTROPIN. Matlock testified that the NCGS has "promotional value" to Genentech (Matlock, CX-8 at 19-20; Matlock, RBPX-18 at 437-38).

340. In addition to the NCSG, complainant's services relating to hGH include seminars and other educational programs, one-on-one educational programs for physicians, provision of free hGH to uninsured patients who are unable to pay for it, and provision of comprehensive reimbursement support for patients (Matlock, CX-8 at 19).

341. Complainant has a "specialized, highly trained sales force" that makes frequent calls on pediatric endocrinologists, nurses, pharmacists and other health care professionals, including " clinical marketing specialists who make such frequent calls" (Matlock, CX-8 at 19).

342. Matlock testified that the "clinical expertise apparent in Genentech's clinical marketing specialists, its NCSG, and its recognized care in ensuring the quality and safety of its hGH are also cited to Genentech by its customers as important in their decision to use Genentech's hGH and is an important competitive consideration" (Matlock, CX-8 at 19).

343. Matlock testified that a conservative statement of the costs of Genentech's sales and marketing activities related to its hGH sales in the U.S. are in 1991; in 1992; and between January and June of 1993 (Matlock, CX-8 at 19).

344. Matlock testified that physicians hold Genentech in very high regard and that physicians "repeatedly have indicate that the reputation of

the manufacturer of hGH is also an important attribute of competition in the U.S. hGH market" (Matlock, CX-8 at 21-22).

345. Kaiser is an example of an HMO that has its own pharmacy (Gross, RBPX-7 at 31-32).

346. In approximately May of 1993, Lilly outbid complainant for a contract with Kaiser (Matlock, RBPX-18 at 152). Kaiser deleted PROTROPIN from its formulary and requested their physicians to prescribe Lilly's Humatrope. (Gross, RBPX-7 at 32). However, as a result of complainant's strong physician relationships, complainant has maintained of its Kaiser sales base. (Gross, RBPX-7 at 32).

347. Grabowski that pediatric endocrinologists are hesitant to switch a patient from one brand of hGH to another during the course of treatment, particularly when there is danger that the patient may have to be switched again within a period of a few months (Grabowski, Tr. at 2095-97).

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349. Genentech believes that BTG will provide a lower level of service than Lilly currently provides (Matlock, Tr. 1374-75).

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354. In "Brand Loyalty, Entry, and Price Competition in Pharmaceuticals after the 1984 Drug Act" (Journal of Law and Economics, October 1992), Grabowski and John Vernon found that the initial price for drugs charged by "new entrants" was generally 30% or more lower than the price charged by the "pioneer" and that, in the case of injectable drugs (as opposed to oral drugs), the pioneers significantly reduced prices in response to the competition (Grabowski, CX-6 at 7). Grabowski testified that this study focused on oral pharmaceuticals (Grabowski, RBPX-5 at 81-82).

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358. In response to questioning concerning Fass' statement in a March 1992 article in Medical Advertising News that "If we end up getting 20% of a $300 million market, that can be a very attractive situation for us. We may be able to get that 20% without having to substantially cut the price" (CX-142), Fass testified that

(Fass, CPX-19 at 319).

359. In addition to BTG and Genentech, Serono Laboratories, Inc. (Serono), Novo, and Kabi Pharmacia AB (Kabi) each has an NDA pending before the FDA for similar hGH products (Matlock, CX-8 at 7). Complainant expects Novo to delay its entry into the market until there is a final determination by the Commission on permanent relief in this investigation (Matlock, CX-8 at 14). Complainant expects Kabi to enter the market in

(Matlock, CX-8 at 14). Complainant anticipates that Serono will enter the market upon approval of its NDA in approximately March 1994 (Matlock, CX-8 at 14).

360. With respect to Novo's entry into the market, Matlock testified as follows:

> As a result of the consent agreement in this matter between Novo and Genentech, Novo will not enter the U.S. hGH market for growth hormone deficiency until July 1, 1994, if then. [I say, "if then" because I understand that there is a probability that by that time there will have been an initial determination on patent issues as they relate to Novo, and Genentech expects these to be affirmative. If that is the situation, it would seem unlikely that Novo would enter the U.S. market in July 1994, as I am told that a final decision would be only about three months later. It would seem that such a period is probably too short to make it worthwhile for Novo to attempt to establish relationships with potential customers and risk having its product taken out of the market three months later.]

(Matlock, CX-8 at 14) (brackets in original).

361. With respect to the applicability of the preceding finding of fact to BTG, Matlock testified at the hearing as follows:

> Q . . . Now, isn't it also true that this initial determination will also address patent issues as they relate to BTG, and that Genentech also expects that the ID, which is scheduled to come out by June, 1994, will be affirmative regarding BTG's infringement?
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> A Based on the conversations I've had with our lawyers, I expect that we believe that it is going to be affirmative, yes.
>
> Q Now, assuming that BTG has not entered into the U.S. market for human growth hormone by July 1, 1994, isn't it fair to conclude that if that's the case, it will be unlikely that BTG will enter the market in the period between July and September, 1994, for the same reasons that you don't expect Novo to do so?
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> * * *
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> A And so the question is, if they haven't started promotional activity -- they already have approval. They could have already had a product made and ready to go, but they just haven't started selling and marketing activity.
>
> Q Just like Novo; that's correct. Just like Novo under the agreement.
>
> A I think as a business person, it's hard for me to believe that if they have already received approval, and they have made product, I'm not sure why they wouldn't have come to market before July.

But assuming they haven't come to market before July, one view would be that they wouldn't come, similar to Novo Nordisk, because they would believe there would be a determination in September that would prevent them from coming to market.

* * *

But if they did decide to come to market in July or December, I would assume that it would be because they would try and gather as much revenue as they could in that short period of time. That would be one of their objectives, if they decided to come to market.

Q But the assumption, Ms. Matlock, is that haven't decided. They are not in the market. And isn't it your view that if they are not in the market, such as Novo, by July 1, 1994, it is unlikely that they enter the market between that period in September, if there is an affirmative initial determination by July, 1994?

A First of all, for Novo, what we've said is that it is unlikely but not impossible that they would enter the market. And I think the same situation holds true for BTG.

Its unlikely that based on an opportunity to come to the market for three months that they would decide to do it. It's not impossible that they would decide to come to market.

So I would say that the situation is fairly similar.

(Matlock, Tr. at 1337-40).

362. [THERE IS NO FINDING 362]

R. Harm To BTG/Balance of Harm

363. Yehuda Sternlicht is BTG's Chief Financial Officer (CFO) and is the person responsible for the preparation of BTG's financial reports and BTG's 1994 budget (Sternlicht, CPX-31 at 4-9).

364. BTG's historical financial data are as follows:

	1988	1989	1990	1991	1992
Tot. Revenue	6,745	4,872	4,307	5,136	6,019
Tot. Expenses	13,550	12,878	10,524	13,066	15,916
Net Loss	(6,805)	(5,561)	(6,217)	(7,930)	(9,797)

(1988-92 data: CX-195 at 21; 1993 data: CX-222 (1993 latest est.).

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390. A March 10, 1993, BTG press release, quoting Fass, stated as follows:

> "Since BTG's inception, we have worked hard to create a rich multi-product pipeline with substantial clinical and commercial promise. Today, that pipeline includes thirteen products. BTG's commercial success does not depend on any single;e product alone. Conversely, and a critical point only now being appreciated more full within our industry, we believe that no single product reversal could at this time seriously jeopardize BTG's projected success."

(CPX-38C-1 at 3).

391. In connection with a May 12, 1993, health care seminar in Baltimore, Maryland, sponsored by the brokerage house Alex, Brown and Sons, BTG issued a press release that stated as follows:

> "Initial approvals and the start of sales of human Growth hormone in Japan and Europe in 1993 should bring BTG to profitability in 1994. The incremental revenues from four other key products listed above as well as revenues expected from the additional six products comprising BTG's near-term pipeline should propel BTG in the coming few years to a position among the most exciting in the industry in terms of its financial prospects," stated Sim Fass, BTG's President and Chief Executive Officer.
>
> "We believe that BTG's pipeline is unmatched in terms of both the number of different products it contains and in the near term projections for their approval and commercialization," said Fass.

(CPX-38-2).

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S. Public Interest

395. Human growth hormone is prescribed for the treatment of the condition of short stature due to growth hormone deficiency, a condition that is not life threatening (Matlock, Tr. at 1424).

396. No patient's use of hGH would be interrupted by the issuance of a TEO due to the fact that BTG is not currently selling the drug in the United States (Fass, RBX-2 at 24).

397. According to complainant's plant controller, John Whiting, complainant has adequate capacity to completely supply the United States market for hGH products (CX-38 at 8).

398. Dr. Barry Sherman was qualified as an expert with respect to the efficacy, safety and potency of recombinant hGH (Tr. at 1257).

399. The FDA requires proof of safety and efficacy before it will approve a drug for commercial sale (Sherman, CX-232 at 4). Complainant's PROTROPIN has been approved by the FDA for use in treating growth hormone deficiency, and complainant's NUTROPIN has been approved by the FDA for use in treating short stature associated with chronic renal insufficiency (Sherman, CX-232 at 4).

400. Before genetically-engineered growth hormone was developed, the supply of hGH was derived from human cadavers (Fass, RBX-5 at 16). Fass stated that it is very difficult and costly to naturally-derived hGH, with the resulting product costing approximately $40,000 per gram (Fass, RBX-5 at 16).

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402. Complainant's associate director of endocrinology and immunology projects, Matlock, testified that when complainant entered the U.S. hGH market with PROTROPIN, it "established its price at a level approximately 25% below the then-prevailing price for hGH extracted from natural sources" (Matlock, CX-8 at 15).

403. Matlock testified that complainant's price for PROTROPIN has remained unchanged since complainant entered the market in 1985 (Matlock, CX-8 at 15).

404. Matlock testified that the Consumer Price Index for all prescription drugs has risen 80% since complainant entered the U.S. hGH market with PROTROPIN in 1985, and that thus, in relative terms, complainant's price for hGH has fallen by approximately 44% compared to the Consumer Price Index. (Matlock, CX-8 at 15).

405. Matlock predicted that even if BTG does not enter the U.S. hGH market, prices will in 1994, 1995 and 1996 over current levels, for a (CX-221).

T. Bonding

406. Louis J. Lavigne, Jr. is complainant's Chief Financial Officer.

(Lavigne, CX-30 at 1).

407. Genentech's 1992 net revenues for U.S. and Canadian sales of its hGH products totaled with U.S. sales accounting for of the total, i.e. (Lavigne, CX-30 at 6, 12).

XII. Conclusions of Law

1. The Commission has in rem jurisdiction and subject matter jurisdiction.

2. Complainant is likely to succeed on the merits with respect to the '980 patent.

3. Complainant, at this time, has not shown that it is likely to succeed on the merits with respect to the '832 patent.

4. Complainant has not shown that it is likely to succeed on the merits with respect to the '619 patent.

5. Complainant will not suffer irreparable harm in the absence of temporary relief.

6. BTG will not suffer harm if temporary relief is granted.

7. The balance of harm, as between complainant and BTG, tips toward neither party.

8. No public interest would be adversely affected if temporary relief is granted.

9. Motion No. 358-1 is denied.

10. Should the Commission grant Motion No. 358-1, complainant should be required to post a bond of 5 percent.

XIII. Initial Determination and Order

Based on the foregoing findings of fact, conclusions of law, the opinion, and the record as a whole, and having considered all of the pleadings and arguments presented orally and in briefs, as well as certain proposed findings of fact, Motion No. 358-1 is denied.

The administrative law judge hereby CERTIFIES to the Commission this initial determination, together with the record consisting of the following:

1. The transcript of the prehearing conference, the hearing and the closing arguments;

2. The exhibits admitted into evidence and the exhibits as to which objection have been sustained; and

3. ALJ Exhibit 1.

The pleadings of the parties filed with the Secretary are not certified, since they are already in the Commission's possession in accordance with the Commission's interim rules.

Further it is ordered that:

1. In accordance with Commission interim rule 210.44(b), all material heretofore marked in camera because of business, financial, and marketing data found by the administrative law judge to be cognizable as confidential business information under Commission interim rule 201.6(a) is to be given in camera treatment continuing after the date this investigation is terminated.

2. Counsel for the parties shall have in the hands of the administrative law judge a copy of this initial determination with those portions containing confidential business information designated in brackets, no later than Wednesday, February 9, 1994. Any such bracketed version shall not be served by telecopy on the administrative law judge. If no such version is received

from a party, it will mean that the party has no objection to removing the confidential status, in its entirety, from this initial determination.

3. Pursuant to Commission interim rule 210.24(e)(17). This initial determination shall become the determination of the Commission thirty (30) calendar days after issuance thereof, unless the Commission modifies or vacates the initial determination within that period.

Paul J. Luckern
Administrative Law Judge

Issued: January 26, 1994