United States District Court,
D. Delaware.

ENZO BIOCHEM, INC,
Plaintiff.
v.
CALGENE, INC,
Defendant.

Civil Action No. 93-110-JJF

June 1, 1998.

Patentee brought action for infringement of patents relating to genetic antisense technology, sought declaratory judgment of invalidity of alleged infringer's patent, and alleged malicious prosecution. Alleged infringer filed counterclaim seeking declaratory judgment that patents were invalid and not infringed. Following bench trial, the District Court, Farnan, Chief Judge, held that: (1) patentee's patents were not infringed; (2) patentee's patents were invalid for failure to meet enablement requirement; (3) alleged infringer's patent was valid; and (4) patentee failed to prove malicious prosecution.

Judgment entered in favor of defendant.

5,272,065. Cited.

Josy W. Ingersoll, John W. Shaw, of Young, Conaway, Stargatt & Taylor, Wilmington, DE, of counsel Richard L. DeLucia, Charles A. Weiss, of Kenyon & Kenyon, New York City, for Plaintiff.

Patricia Smink Rogowski, of Connolly, Bove, Lodge & Hutz, Wilmington, DE, of counsel William F. Lee, James L. Quarles III, William G. McElwain, and David B. Bassett, of Hale and Dorr, Washington, DC, for Defendant.

OPINION

FARNAN**, Chief Judge.**

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I. INTRODUCTION

This is a patent case involving genetic antisense technology. Plaintiff Enzo Biochem, Inc. ("Enzo") brought this action against Defendant Calgene, Inc. ("Calgene") for infringement of two patents for which it is the exclusive licensee (D.I.363). Enzo claims that Calgene infringes United States Patent Number 5,190,931 (the " "1 Patent") and United States Patent Number 5,208,149 (the " '149 Patent") by its production of the FLAVR SAVR(R) brand tomato. Enzo also seeks a declaratory judgment finding Calgene's patent, United States Patent Number 5,107,065 (the "Calgene '065 Patent") invalid and unenforceable on the grounds of misuse, anticipation and obviousness. Finally, Enzo alleges malicious prosecution by Calgene as a result of Calgene's litigation against Enzo in California. (D.I. 1 at 2, 44-46).

Defendant Calgene has counterclaimed, seeking a declaratory judgment that the "1 Patent, the '149 Patent and a third Enzo patent, United States Patent Number 5,272,065 (the "Enzo '065 Patent") are invalid, unenforceable and not infringed. (D.I. 54 at 367). Calgene contends that Enzo's patents are invalid on the grounds of non-enablement, anticipation, obviousness and inequitable conduct before the United States Patent and Trademark Office ("PTO"). Additionally, Calgene defends the validity of the Calgene '065 Patent, although it alleges that the Court has no jurisdiction to decide the issue. (D.I.367). Both parties seek an award of a attorney's fees, claiming that the case is exceptional. (D.I. 363; D.I. 369).

In the first patent infringement action filed by Enzo against Calgene, Enzo alleged infringement of its "1 Patent only. (D.Del.C.A. 93-110-JJF). In the second infringement action Enzo filed against Calgene, it

alleged infringement of its '149 Patent. (D.Del.C.A.94-57-JJF). Because both actions involved similar factual and legal issues, the Court ordered the actions to be consolidated on October 7, 1994. (D.I.322).

The Court bifurcated the liability and damages issues for purposes of trial and conducted a bench trial on the issues of infringement, willful infringement, validity, enforceability, and attorney's fees in April, 1995. (D.I.464). FN1 Pursuant to Federal Rule of Civil Procedure 52, the Court issued an Opinion setting forth its findings of fact and conclusions of law. Shortly thereafter, the parties informed the Court of an inconsistency in its Opinion. In order to prevent confusion on appeal, the Court withdrew its Opinion.

FN1. In its Amended Complaint (D.I. 363 at 20-22), Enzo asserted a claim of scientific misconduct against Dr. Izant and Dr. Weintraub. At the beginning of the trial, however, when Enzo voluntarily dismissed several claims that it had alleged against Calgene, no mention was made of its scientific misconduct claim, although Calgene believed it was still an issue and addressed it in its opening statement. Enzo presented several witnesses and one expert report at trial to support its claim; however, it did not present its claim of scientific misconduct as a separate issue in its post-trial briefs. (*See, e.g.,* D.I. 525 at 111-112, 113 (discussing the scientists' alleged behavior under a section concerning anticipation and obviousness)).

Enzo alleges that Dr. Izant and Dr. Weintraub "trimmed", "cooked", and "forged" their experiments to arrive at solutions that they wanted, and failed to run "blinds" to insure that the results were accurate. (Gilbert Tr. at 1059; D.I. 525 at 110-112, 113). Enzo points to a litany of experiments reported in Dr. Izant's notebooks in which Enzo claims he altered results. For example, Enzo claims that Dr. Izant changed numbers in one experiment to reduce the number of TK positive cells, intending to rig the experiment to produce the result he wanted. (D.I. 525 at 115-116). Enzo also claims that the scientists mischaracterized their findings in an article they published in the *Cell* journal, in which they stated that certain flipped constructs regulated gene expression but others did not, while their experiments showed otherwise. (D.I.118-119).

The Court concludes that Enzo has failed to establish its claims so as to persuade the Court that misconduct affecting the results and conclusions of Dr. Izant and Dr. Weintraub's research occurred. Thus, while the Court agrees that Dr. Izant's notebook contained some inconsistencies, these inconsistencies are insufficient to support a finding of scientific misconduct.
Since withdrawing its Opinion, the Court has conducted a full review of the record and re-read the briefs submitted. As a result of this review, the Court has determined that its claim interpretation analysis omitted a discussion of the meaning of the disputed term "complementary" in Claim 1 and Claim 34 of the "1 Patent. In the instant Opinion, the Court will include a discussion of this issue in its claim interpretation analysis. This Opinion shall constitute the Court's findings of fact and conclusions of law in this case, superseding any previous findings and conclusions.

A. *Description of Parties*

Enzo is a company which seeks to find and create new technologies for development into products with biomedical and other scientific applications. FN2 (Engelhardt Tr. at 680). Enzo is comprised of three wholly owned subsidiary companies, including: Enzo Labs, a full service clinical reference laboratory; Enzo Diagnostics, a company involved in developing technology to identify pathogens by genetic analysis; and Enzo Therapeutics, a development company. (Engelhardt Tr. at 679).

FN2. Enzo is a corporation organized and existing through the laws of the State of New York. Enzo has offices in Farmingdale, New York and New York City, New York.

Enzo is the exclusive licensee of the "1 Patent, the '149 Patent and the Enzo '065 Patent. The "1 Patent

issued to Dr. Masayori Inouye on March 2, 1993 and claims a method of controlling the function of any gene in any cell through genetic antisense. (PX 730). The '149 Patent issued to Dr. Inouye on May 4, 1993, and is an improvement patent claiming a method of genetic antisense in stable stem and loop structures. Dr. Inouye is also the inventor on the Enzo '065 Patent, issued on December 21, 1993, which also claims a method of regulating genes through genetic "antisense" technology. Enzo licensed these three patents from the Research Foundation of the State of New York and paid approximately three-quarters of a million dollars for them. (Engelhardt Tr. at 681).

Calgene is an agricultural biotechnology company with offices and facilities in California, Illinois, Mississippi and Florida.FN3 (Knauf Tr. at 1849). Calgene was founded in 1980, and since that time has focused its business strategy on the use of transgenic plant technology in agricultural applications. (Knauf Tr. at 1852-53). Calgene's genetically engineered products include vegetable oils, cottonseed and the FLAVR SAVR tomato. Calgene is the assignee of United States Patent Number 5,107,065, issued to Christine Shewmaker, et al., on April 21, 1992. The Calgene '065 Patent claims antisense regulation of gene expression in plants. The technology of the Calgene '065 Patent was critical in the development of Calgene's FLAVR SAVR tomato, a product which boasts a delayed ripening process. (Knauf Tr. at 1858-61).

FN3. Calgene is a corporation organized and existing under the State of Delaware. Calgene's principle place of business is in Davis, California.

B. *Jurisdiction*

The Court has jurisdiction over the parties and the subject matter of this patent dispute pursuant to 28 U.S.C. s. 1338(a) (1995). The Court has jurisdiction over the asserted counterclaims pursuant to 28 U.S.C. s.s. 1338(a) and 2201(a) (1995). Additionally, jurisdiction is proper under 28 U.S.C. s.s. 1331 and 1332 (1995).

II. SCIENTIFIC BACKGROUND

A. *Basic Concepts Relating to Gene Regulation*

The patents involved in this litigation concern "gene regulation," in which the function or "expression" of a gene is manipulated. Both parties presented expert testimony on the basic concepts and principles of gene regulation.

The Court has based its findings of fact with respect to the underlying science on the testimony of the experts the parties presented at trial. Regardless of what knowledgeable scientists in the field might believe is the relevant science, the function of the Court is to make findings of fact and draw conclusions of law based only on the evidence presented at trial. FN4 Accordingly, from the record evidence, the Court understands the underlying science relevant to the instant patents as follows.

FN4. The Court commends and thanks counsel, particularly Mr. Lieberman and Mr. Lee, for their exceptional and highly professional presentations.

1. DNA, RNA, Transcription and Translation

A "gene" is a "nucleotide sequence," such as deoxyribonucleic acid ("DNA"), which provides a code for a certain characteristic of an organism. (Green Tr. at 92; Falkinham Tr. at 1426). DNA makes up the genes of virtually every organism, and the genes determine the characteristics of the organism. (Green Tr. at 92). A single strand of DNA is made up of subunits, termed "nucleic acids" or "bases", which link together to form

a long chain. (Falkinham Tr. at 1408-09). These subunits are Adenine, Thymine, Guanine and Cytosine. Depending on the sequence in which they occur, they define every protein in an organism. (Falkinham Tr. at 1410).

Two single strands of DNA are complementary, and can link up according to "base pairing rules," where their bases pair together to form a double helix. (Green Tr. at 94). The bases can only link together in a certain way. For example, Adenine can link only with Thymine, and Guanine can link only with Cytosine. (Green Tr. at 94; Falkinham Tr. at 1410, 1411-12). Thus, the sequence in which the bases occur on one strand of DNA will dictate the required sequence of the second strand if they are to form a double helix. (Green Tr. at 94). Two strands linked together in this fashion are said to be "complementary" to one another. (Green Tr. at 94).

DNA tells the cells what proteins to make through a two-step process of "transcription" and "translation." (Green Tr. at 92, 95; Falkinham Tr. at 1411). In the first step, transcription, the DNA transfers information to an RNA polymerase molecule, which makes a "messenger RNA" ("mRNA") from the DNA, which in turn shuttles that information out into the cell. The DNA double helix opens up to permit a single strand of RNA polymerase to attach to one of the DNA strands. (Falkinham Tr. at 1414-15). Like DNA, RNA is a long chain of linking subunits, except that RNA contains the subunit Uracil instead of Thymine. When the RNA polymerase links with the single strand of DNA according to base pairing rules, the RNA's Uracil pairs with Adenine instead of the DNA's Thymine. (Green Tr. at 95).

The RNA does not arbitrarily attach to the DNA, however, but begins reading at a "promoter sequence" and stops at a "terminator sequence," both specified by the nucleic acid. (Green Tr. at 99; Falkinham Tr. at 1413). The promoter is the portion of the DNA construct which facilitates the start of the transcription of the RNA. (Green Tr. at 114.; Falkinham Tr. at 1413). The transcription termination segment is a configuration of bases on the fragment of the DNA construct which signals the end point of the RNA molecule. (Green Tr. at 114; Falkinham Tr. at 1413). The genetic message "stops" at the terminator sequence or segment. (Falkinham Tr. at 1414).

In the second step, translation, a ribosome attaches to the released mRNA to construct a protein from the information in the mRNA. (Green Tr. at 96-97). A protein is comprised of a series of amino acids, which are themselves comprised of a configurations of bases, similar to those found in DNA. (Green Tr. at 97). The ribosome reads the information in the mRNA to determine which amino acids, and ultimately which protein, it is to create. (Green Tr. at 97).

During translation, as the mRNA transfers its information about the amino acids into the ribosome, another molecule, the transfer RNA ("tRNA"), brings one of these amino acids that the mRNA has called for into the ribosome. (Green Tr. at 98). A second tRNA will bring the next amino acid, which links to the first, and a third tRNA will bring the third, which links to the second, and so forth until a complete chain forming the protein identified by the information in the mRNA is created. (Green Tr. at 98).

DNA and RNA may also form a "stem and loop" structure. A stem and loop structure is a single strand of nucleic acid that folds back onto itself, creating a double-stranded loop according to base pairing rules. (Engelhardt Tr. at 811; Green Tr. at 96). The stem and loop structure is not permanent, but instead undulates by repeatedly forming and collapsing. (Engelhardt Tr. at 811). A ^G measurement measures the stability of the stem and loop: the higher the negative 'G, the more stable the stem and loop. (Engelhardt Tr. 811).

2. Differences Between Prokaryotes and Eukaryotes

The primary difference between prokaryotic cells and eukaryotic cells is that a prokaryotic cell does not

have a nucleus or nuclear membrane, while a eukaryotic cell does. (Falkinham Tr. at 1419). One result of this difference is that a prokaryotic cell can commence translation of an mRNA even before the transcription process has ended. (Falkinham Tr. at 1415). In other words, while the RNA polyermase is creating the mRNA at one end, the ribosome is reading the information in the mRNA on the other. (Falkinham Tr. at 1415).

Unlike prokaryotic cells, however, the mRNA in eukaryotic cells cannot undergo transcription and translation at the same time. Transcription in eukaryotic cells occurs in the nucleus of the cell, but translation occurs in the cytoplasm of the cell, so that the mRNA must pass through the nuclear membrane between the two steps. (Falkinham Tr. at 1423-25).

Another distinction between prokaryotes and eukaryotes is that eukaryotic RNA has "introns". (Knauf Tr. at 1886). Introns are intervening sequences that appear in the middle of a gene, and are similar to "a sequence of nonsensical letters or words which disrupted the normal flow of a sentence". (Falkinham Tr. 1423). Eukaryotes can "clip-out" these sequences and splice the ends of messages back together again. (Falkinham Tr. at 1423).

3. Antisense

Antisense technology regulates the expression of a gene by inhibiting either the transcription or translation of the coding. (Falkinham Tr. at 1427). For example, in naturally occurring antisense, the "sense" element is the single strand of DNA which contains the code that is transcribed into the mRNA, and that DNA strand makes sense in terms of what the message has to contain. (Green Tr. at 102). The code of the complementary strand of DNA would not make sense in terms of the transcription process with that mRNA. Therefore, the opposing strand of the DNA in the double helix is called the "antisense." (Green Tr. at 103). Thus, when the DNA is wrapped together as a double helix, its sense and antisense strands essentially shut off the expression of the other, until the double helix opens up and the gene function again begins. (Green Tr. at 108)

In artificially created antisense, the function of the DNA or RNA can be regulated by the introduction of a non-complementary strand. For example, mRNA can be manipulated through the introduction of an non-complementary RNA molecule. The non-complementary RNA would not make sense, and accordingly would shut off the function of the mRNA. (Green Tr. at 103). Antisense can also be introduced that attaches to the DNA sense strand, blocking the formation of the mRNA. (Green Tr. at 108).

B. ***Antisense Experimentation in Dr. Inouye's Lab***

Dr. Inouye and his laboratory conducted experiments attempting to regulate gene expression by creating antisense constructs. (Green Tr. at 107). Dr. Pamela Green and Dr. Jack Coleman conducted many of the experiments in Dr. Inouye's laboratory during this time. (Green Tr. at 116, 188).

The experiments in Dr. Inouye's lab concentrated on three genes found in *Escherichia coli* (" *E.coli* "), a prokaryotic bacterium. (Green Tr. at 108-09). These genes included the outer membrane protein A ("ompA"), the outer membrane protein C ("ompC") and lipoprotein ("lpp"). (Green Tr. at 107). *E. coli* has been a model system for molecular experimentation since the 1940's, used because it can be representative of the functions of larger, more complex organisms. (Green Tr. at 109-11). Moreover, basic principles discovered from experiments in *E. coli* can readily be extrapolated and applied to other organisms. (Green Tr. at 110).

Dr. Inouye's goal was to create antisense constructs which would shut off the expressionof ompA, ompC and lpp. (Green Tr. at 114). To achieve this goal, a cloning vector was set up by inserting a promoter and

terminator into a plasmid (a circular piece of DNA). The promoter facilitated the start of transcription and the terminator signaled the end. (Green Tr. at 114). Second, a segment of the target gene would be taken and flipped with respect to its usual orientation. (Green Tr. at 115, 125). The promoter segment and termination segment would remain in ordinary position and order. (Green Tr. at 246). Third, the flipped gene segment would then be inserted in between the promoter and terminator of the cloning vector. (Green Tr. 115). Finally, the antisense construct would then be introduced into the *E. coli* bacteria through a method called transformation. (Green Tr. at 115).

Dr. Inouye's lab termed the antisense construct created by the flipped gene construct "messenger interfering complementary RNA" ("micRNA"). (Green Tr. at 107, 115). Introduction of the micRNA into the target cell had the expected result of stopping the function of the mRNA and shutting off the target gene that made the mRNA. (Green Tr. at 116). The mRNA, now bound to the micRNA, could no longer function normally, because the micRNA inhibited the expression of the gene. (PX 730, col. 3, lines 27-37).

The experiments in Dr. Inouye's lab were not without failures, however. Over a ten-year span, Dr. Inouye failed to regulate any other genes except for ompA, ompC and lpp, reporting ten or twelve failures in other *E. coli* genes, as well as yeast, oncogenes and eukaryotic cells. (Inouye Tr. at 357, 450-51, 458-460, 464-465).FN5 In addition, antisense regulation of the gene expression by micRNA in the ompA, ompC and lpp genes themselves was not always consistent, as introduction of antisense RNAs, intended to regulate the ompC gene, also shut off the function of the lpp gene, and vice versa. (Green Tr. at 117). Moreover, the success of the inhibition levels of the functions of the ompA, ompC and lpp genes often increased with the introduction of additional genes. (Green Tr. at 119). Dr. Inouye's lab failed to regulate eukaryotic genes, including the SRV oncogene (Inouye Tr. at 458); the Kirsten oncogene (Inouye Tr. at 459) and thymidine kinase (Inouye Tr. at 460). However, at trial, Dr. Inouye explained that his laboratory failures in applying genetic antisense to other genes were just unsuccessful or incomplete experiments by graduate students with insufficient skill in the organism or gene sought to be regulated. (Inouye Tr. at 356-357, 464-65, 492-93).

FN5. Dr. Green also conducted experiments to see if Dr. Inouye's invention worked in eukaryotic cells, specifically the tomato mosaic virus. However, she left the laboratory before she was able to complete her work. (Green Tr. at 135-36). During Dr. Green's tenure in Dr. Inouye's lab, on September 28, 1984, she submitted a proposal grant outlining her research. Although she noted that antisense regulation in plants looked feasible, she did not claim it was obvious or easy. (Green Tr. at 137, 152-54, 169; PX 262).

Dr. Green testified at trial, and her laboratory notebooks confirmed that the date of conception of the antisense idea as developed in Dr. Inouye's lab was June 3, 1983. The first step undertaken by Dr. Green in executing this idea occurred on August 26, 1983, and the first demonstration of antisense inhibition of ompA or ompC occurred sometime between August 26, 1983 and December 29, 1983. (Green Tr. at 211-12, 221).

Dr. Inouye's initial research efforts in the area of genetic antisense were first reported in an article published in the *Japanese National Academy of Sciences* in December, 1983. In the article, Dr. Inouye described natural antisense inhibition of ompF by micF RNA. (Inouye Tr. at 1475-76; PX 182). This article, published before his work in ompA, ompC and lpp, examined the proposition that micF RNA blocked translation of the ompF mRNA. (Falkinham Tr. at 1477-78). Dr. Inouye published the results of his laboratory's work in ompA, ompC and lpp in *Cell* in June 1984.FN6 (Green Tr. at 120). He next co-authored a review article with Dr. Green in 1985 discussing the roles of anti-sense RNA that were available at that time in prokaryotes and eukaryotes. (Green Tr. at 139; PX 344).

FN6. *Cell* is a scientific journal that publishes articles in molecular biology and biochemistry. (Green Tr. at 121).

C. ***Dr. Izant and Dr. Weintraub's Work in Antisense Technology***

Dr. Izant and Dr. Weintraub also worked on artificial antisense to regulate the expression of a gene, but concentrated on eukaryotic genes instead of prokaryotic ones. Dr. Weintraub was a respected scientist, and a member of the Basic Sciences Division of the Fred Hutchinson Cancer Research Center. (Weintraub Dep. at 73; Reeder Tr. at 2055-56; Silverstein Tr. at 1317). Dr. Jonathan Izant was a post-doctoral fellow in Dr. Weintraub's laboratory from the middle of 1982 until 1986. (Izant Dep. at 14, 15, 69).

Dr. Weintraub and Dr. Izant conceived of the idea to regulate expression of TK genes in mouse cells by genetic antisense in 1982. In the spring of 1982, before Dr. Izant actually began working for Dr. Weintraub, they met and discussed the idea of inhibiting genes by introducing complementary nucleotide sequences which would bind with a target. (Weintraub Dep. at 302-05; Izant Dep. Vol. I at 18-19). In August of 1982, after arriving at Dr. Weintraub's lab, Dr. Izant began experiments designed to regulate the expression of TK genes in mouse cells. (Izant Dep. Vol. I at 24-26; DX 82 (lab notebook)). Dr. Weintraub's notebook indicates that between October 27, 1982 and November 1, 1982 he was experimenting with the "reverse orientation of TK structural gene between its promoter and a poly-adenylation signal ... to produce antisense transcripts as potential anti-message." (DX 82; Izant Dep. II at 21-33; (lab notebook)). Finally, in November of 1982, Dr. Izant began experimenting with a series of DNA constructs, including an antisense TK construct, and by December 13, 1982, he had made an antisense construct containing a promoter, a flipped HSV TK gene, and a polyadenylation signal. (Izant Dep. Vol. I at 44-45; DX 82 at 121 (lab notebook)).

From November 1982 through 1983, Dr. Izant experimented with co-microinjections of sense and antisense TK genes into TK minus mouse cells. (Weintraub Dep. at 221, 277-80, 404-05). He also experimented with the idea of stably incorporating an antisense DNA into the cell's DNA. (Izant Dep. Vol. I at 16; Weintraub Dep. at 167-70; DX 28 (*Cell* paper) at 1010, Table 2). Dr. Weintraub also conducted experiments to confirm Dr. Izant's initial successes. (Weintraub Dep. at 310-13; DX 39 (*Science* paper)). Both Dr. Izant and Dr. Weintraub reported rapid successes, with Dr. Izant first reporting inhibition of the TK gene as early as January 29, 1983. (Izant Dep. Vol. II at 445-49; DX 82 at 147 (lab notebook)).

Dr. Izant and Dr. Weintraub published the results of their antisense work in the April 1984 issue of the scientific journal *Cell* and the July 1985 issue of the scientific journal *Nature*. (Izant Dep. Vol. I at 16; Weintraub Dep. at 167-70; DX 28 (*Cell* paper) at 1010, Table 2). They also gave a presentation on their antisense work at the Gordon Conference on July 29, 1983. (Izant Dep. Vol. I at 67; Harland Dep. at 24-25). Moreover, they documented their successes in grant applications to the National Institute of Health ("NIH") on January 5, 1983 and May 18, 1983. (Weintraub Dep. at 645-46; NIH grant application, DX 81 p. HW0182; DX 100 (letter to NIH)). They started work on their patent application in the fall of 1983, and filed the patent application in January of 1985.

Dr. Izant and Dr. Weintraub became aware of Dr. Inouye's work in antisense after their *Cell* paper was accepted for publication, but before it was actually published, which was sometime between December 1983 and April 1984. (Izant Dep. Vol. I at 196, 527-28; Weintraub Dep. at 193-95). Dr. Izant also become aware of advertisements published by Dr. Inouye in the November 17, 1983 issue of *Nature* magazine and the December 1983 issue of *Cell*.

D. ***The Antisense Work of Other Scientists***

Many scientists who undertook research involving antisense technology experienced difficulty in achieving antisense in eukaryotic cells. (*See, e.g.,* Wold Dep. at 84 (work in Thymidine kinase); Crowley Dep. at 54-55 (work in Dictyostelium discoideum-slime mold); Davis Dep. at 25-30 (work in saccharomyces-baker's

yeast)). For example, Dr. Barbara Wold, an Enzo witness, testified at her deposition that there were many instanceswhere antisense did not work to regulate the expression of a gene. (Wold Dep. at 84). Dr. Wold published an article in *Cell* with Dr. Stuart Kim, in which she postulated that a phenomena termed "posttranscriptional aberrant processing" existed in eukaryotic cells, but not prokaryotic cells. (Wold Dep. at 33-35, 49-51; *see also* Drs. Barbara Wold & Stuart Kim, *Stable Reduction of Thymidine Kinase Activity in Cells Expressing High Levels of Antisense RNA, Cell,* Vol. 42, pp. 129-38, Aug. 1985). Dr. Wold testified that to insure that antisense would work in a given gene would require experimentation on a case-by-case basis. (Wold Dep. at 50-51).

Other scientists followed in the footsteps of Dr. Weintraub and Dr. Izant. For example, Dr. Weinberg, another consultant to Enzo, had attended the Weintraub presentation at the Gordon Conference. (Weinberg Dep. at 6-7; Weintraub Dep. at 203). His laboratory conducted experiments in September 1983 to inhibit an oncogene by antisense, which he described in his notebooks as the "Weintraub Experiment." (Weinberg Dep. at 145).

E. ***The Enzo Patent Prosecution***

1. Patent Applications

Dr. Inouye filed his original patent application for the "1 Patent on October 20, 1983, disclosing only the example of natural antisense work with micF. (DX 3 at tab 1). He filed a second application on March 1, 1984, in which he disclosed his work with ompA, ompC and lpp. (DX 5 at tab 1). The two patent applications were prosecuted separately until they were combined into a single application in 1989, which ultimately resulted in the issuance of the "1 Patent. (DX 7 at tab 27). The only successful examples of antisense provided in the patent application were the work done by Dr. Green and Dr. Coleman in the ompA, ompC, and lpp genes, as well as the original work done by Dr. Inouye in the micF gene. (Green Tr. at 197, 230). Dr. Inouye later filed continuation and divisional applications which led to the issuance of the Enzo '065 and '149 Patents.

2. Prosecution History

The PTO rejected Dr. Inouye's patent applications ten times during prosecution on the grounds of non-enablement, citing its concerns that the technology was too unpredictable for application in other cells besides *E. coli*. The PTO also stated its belief that the contribution of the invention to the relevant technology was too small for such a broad protection of all genes in all cells. (*See, e.g.,* Examiner's Action to '282, No. 585282, at 3-4 (Dec. 10, 1985); D.I. 218 at 223-250).

Dr. Inouye responded to the PTO's rejections by stating that the broad applicability of the invention to all genetic material had already been established, citing several articles that used artificial antisense to regulate organisms other than *E. coli*. (DX 5, tab 7 at 4-6). Neither Dr. Inouye nor Enzo disclosed to the PTO Dr. Inouye's failures with regard to regulating other genes besides those disclosed, including other *E. coli* genes, as well as yeast and eukaryotic cells. In contrast, Dr. Inouye's November 15, 1989 patent application claimed that his invention permitted anyone to construct an artificial mic system to regulate the expression of any specific gene in *E. coli,* including yeast. (Inouye Tr. at 451; DX 7 at 598, tab 1 at 7, 8).

Dr. Inouye and Enzo ultimately overcame the rejections of the PTO by filing the declaration of Dr. Saul Silverstein on October 2, 1990. (Hoscheit Tr. at 649; Joint Exh. 1C, tab 7A). Dr. Silverstein's declaration asserted that Dr. Inouye's invention was a general principle that could be applied without undue experimentation to all genes in all cells, and that it worked so well that no reference disclosed an inoperable application of antisense RNA. (Joint Exh. 1C, tab 7A at 14-15).

3. Dr. Inouye's Actions During Prosecution

In 1988, during the prosecution of the patents, Dr. Inouye published a review article in which he disclosed that his lab had failed to regulate the expression of other *E. coli* genes by antisense RNAs. (DX 13; Masayori Inouye, *Antisense RNA: its functions and applications in gene regulation-a review,* at 30 (*Nature,* June 15, 1988); Tr. at 454-476). Moreover, he disclosed in this article that although successful reports existed on antisenseRNA regulation in mammalian cells, there had been no successful report in yeast. *Antisense RNA, supra,* at 30. Dr. Inouye theorized that the reasons for the failures could be the instability of the individual RNAs of the individual cells, and concluded that it "remained to be seen how effectively the micRNA immune system could work in plants and animals". *Id.* at 30, 32.

In April of 1990, six months before the October 1990 patent application, Enzo sought federal funds from the NIH. The language of the NIH application asserted that "[d]espite ... considerable progress, there are no consistent ways in which to reliably generate an effective antisense gene for use in the inhibition of an endogenous or exogenous gene." (*Antisense Induction of Disease Resistance,* Department of Health and Human Services, Small Business Innovation Research Program, Phase II Grant Application, at 18 (April 1, 1990); DX 148 at 18). However, at trial, Dr. Inouye testified that he had not disclosed this same opinion to the PTO. (Inouye Tr. at 480). It is significant that in his initial application to the NIH, Dr. Inouye had sought over $700,000 to study whether antisense regulation would be successful in eukaryotic cells. (*See* DX 69; Inouye Grant Application, at 48).

F. ***The Calgene Patent Prosecution***

Calgene's FLAVR SAVR tomato is unique in that it slows the ripening process of tomatoes on the vine by inhibiting the enzyme polygalacturonase ("PG") through the use of antisense technology. (Knauf Tr. at 1859-60). Dr. Vic Knauf, a Calgene scientist, began research directed at applying antisense to plants in 1984 after hearing about the work of Dr. Weintraub. (Knauf Tr. at 1865, 1877). On December 12, 1985, Calgene scientists released a document in which they disclosed their antisense work in plants. (Knauf Tr. at 1879). Although Calgene initially considered plant antisense work to be a risky investment, Dr. Knauf and forty other scientists continued to work on it (Knauf Tr. at 1874, 1877), and by mid-to late-1986, the entire project pulled together. (Knauf Tr. at 1910). In 1988, Calgene's scientists published a paper describing the inhibition of expression in plants through antisense. (Knauf Tr. at 1892).

Calgene invested approximately $20 million in research and development over a twelve year period to develop its FLAVR SAVR tomato. Calgene submitted its first patent application for its FLAVR SAVR tomato in September 1987, which was approved by the Patent and Trademark Office ("PTO") on April 21, 1992, resulting in the issuance of the Calgene '065 Patent. (DX 2; PX 589). After the Calgene '065 Patent issued, at least three different companies negotiated licenses with Calgene. (Knauf Tr. at 1864-65).

G. ***Prior Litigation Between Enzo and Calgene***

During late 1992 and early 1993, Calgene was preparing for a public offering of its securities. (PX 664). During this period, Enzo released press statements on three different occasions announcing that Enzo was in the process of obtaining a broad antisense patent that would cover Calgene's products. (Salquist Dep. at 22). Mr. Salquist, the Chief Executive Office of Calgene, testified that he believed the Enzo press releases were issued for the sole purpose of damaging Calgene. Id. Calgene offered expert testimony that Enzo's actions adversely affected the sale price of its stocks. (Salquist Dep. at 123-124; Redington Dep. at 166, 177-78, 180-81; Ford Dep. at 17-18, 36, 43-44; Anderson Dep. at 7). In this regard, the witnesses testified that Calgene stock prices dropped from over $20 a share in the beginning of January 1993 to $15 by the end of January due to the activities of Enzo, including the press releases. (Salquist Dep. 135-136).

In response to Enzo's activities, on February 5, 1993, Calgene filed a lawsuit against Enzo in United States District Court in California, alleging interference with its stock price on four state law grounds.FN7 Calgene

also sought a declaratory judgment to invalidatethe Enzo "1 Patent which had not yet issued. (DX 85). One month later, Enzo issued a press release announcing the issuance of its "1 Patent for genetic antisense technology (PX 731), and on the following day, March 3, 1993, Enzo sued Calgene in this Court. (PX 723A). The district court in California dismissed Calgene's declaratory judgment action in deference to the patent case pending in this Court, which Calgene unsuccessfully appealed. (DX 88 (Order after hearing 6/21/93); PX 723A). Calgene then filed a motion to dismiss with prejudice the remaining claims in California, which was granted in August 1994.

FN7. These claims included: interference with prospective economic advantage, tortious interference with business advantage, negligent interference with prospective economic advantage and unfair competition. (DX 85).

III. INFRINGEMENT

Enzo claims that Calgene's FLAVR SAVR tomato infringes both the Enzo "1 and '149 Patents. (D.I. 525 at 164). Calgene asserts that it has not infringed either patent. Although Enzo does not claim that Calgene infringes Enzo's '065 Patent, Calgene has counterclaimed for a declaratory judgment seeking a declaration that Calgene's FLAVR SAVR tomato does not infringe Enzo's '065 Patent. (D.I. 54).FN8

FN8. In addition to counterclaiming that Calgene has not infringed Enzo's '065 Patent, Calgene has also counterclaimed seeking a declaratory judgment that Enzo's '065 Patent is invalid and unenforceable. Although the parties presented no real evidence pertaining to Enzo's '065 Patent, Calgene contends that the Court's findings regarding the "1 Patent should apply to Enzo's '065 Patent. Because of a lack of presentation of evidence on the counterclaim issues pertaining to Enzo's '065 Patent, the Court has not independently considered Calgene's assertions of non-infringement, invalidity and unenforceability of Enzo's '065 Patent.

A. *Establishing an Infringement Claim*

[1] A patent is infringed when a person "without authority makes, uses or sells any patented invention, within the United States during the term of the patent...." 35 U.S.C. s. 271(a) (1995). The patent owner has the burden of proof, and must meet its burden by a preponderance of the evidence standard. SmithKline Diagnostics, Inc. v. Helena Lab. Corp., 859 F.2d 878, 889 (Fed.Cir.1988) (citations omitted). The preponderance of the evidence standard is met when a party provides evidence regarding a certain issue and that evidence is more convincing than the evidence offered in opposition to the issue. Hale v. Dep't. of Transp., F.A.A., 772 F.2d 882, 885 (Fed.Cir.1985) (citations omitted).

[2] [3] [4] [5] A patent owner may prove infringement under either of two theories: literal infringement or the doctrine of equivalents. Under the theory of literal infringement, infringement occurs where each element of at least one claim of the patent is found in the alleged infringer's product. Panduit Corp. v. Dennison Mfg. Corp., 836 F.2d 1329, 1330 n. 1 (Fed.Cir.1987); Robert L. Harmon, *Patents and the Federal Circuit* 195 & n. 31 (3d ed.1994). A claim in a patent can only be infringed if it reads on each and every element of the alleged infringer's product. American Hoist & Derrick Co. v. Manitowoc Co., Inc., 603 F.2d 629, 630 (7th Cir.1979); *see also* Amstar Corp. v. Envirotech Corp., 730 F.2d 1476, 1484 (Fed.Cir.1984), *cert. denied,* 469 U.S. 924, 105 S.Ct. 306, 83 L.Ed.2d 240 (1984) (infringement avoided only if element present in alleged infringing process absent in patented invention); Hormone Research Found., Inc. v. Genentech, 904 F.2d 1558, 1562 (Fed.Cir.1990), *cert. dismissed,* 499 U.S. 955, 111 S.Ct. 1434, 113 L.Ed.2d 485 (1991) (infringement only if each claim or equivalent found in accused invention). If a patent has a series of claims, and one claim is infringed, then the entire patent is infringed. Panduit, 836 F.2d at 1330 n.

1. Under the theory of the doctrine of equivalents, however, infringement may be established even where elements in the claimed invention are missing from the alleged infringer's product, if the "accused device performs substantially the same function in substantially the same way to achieve substantially the same result as the claimed device." Graver Tank & Mfg. Co. v. Linde Air. Prods. Co., 339 U.S. 605, 608, 70 S.Ct. 854, 94 L.Ed. 1097 (1950); Warner-Jenkinson Company, Inc. v. Hilton Davis Chemical Co., 520 U.S. 17, 117 S.Ct. 1040, 137 L.Ed.2d 146 (1997) (declining to overrule *Graver Tank*); Malta v. Schulmerich Carillons, Inc., 952 F.2d 1320, 1325 (Fed.Cir.1991).

[6] To find infringement under either theory, the Court must undertake a two-step process. First, it must interpret the claims at issue by evaluating the language of the claims ("claim interpretation"). Miles Lab., Inc. v. Shandon, Inc., 997 F.2d 870, 876 (Fed.Cir.1993), *cert. denied,* 510 U.S. 1100, 114 S.Ct. 943, 127 L.Ed.2d 232 (1994). Claim interpretation is a question of law. Markman v. Westview Instruments, Inc., 52 F.3d 967, 977-978 (Fed.Cir.1995), *aff'd,* 517 U.S. 370, 388-390, 116 S.Ct. 1384, 134 L.Ed.2d 577 (1996).

[7] [8] [9] When construing the claims of a patent, a court considers the literal language of the claim, the patent specification and the prosecution history. Markman, 52 F.3d at 978. A court may consider extrinsic evidence, including expert and inventor testimony, dictionaries, and learned treatises, in order to assist it in construing the true meaning of the language used in the patent. Id. at 980 (citations omitted). A court should interpret the language in a claim by applying the ordinary and accustomed meaning of the words in the claim. Envirotech Corp. v. Al George, Inc., 730 F.2d 753, 759 (Fed.Cir.1984). However, if the patent inventor clearly supplies a different meaning, the claim should be interpreted accordingly. Markman, 52 F.3d at 980 (noting that patentee is free to be his own lexicographer, but emphasizing that any special definitions given to words must be clearly set forth in patent). If possible, claims should be construed to uphold validity. In re Yamamoto, 740 F.2d 1569, 1571 & n. * (Fed.Cir.1984) (citations omitted).

The second step to determine infringement requires a court to compare the accused products or patented claims with the properly construed claims of the patent at issue to determine whether the accused products or processes infringe on the patent under either the theory of literal infringement or under the theory of the doctrine of equivalents ("infringement analysis"). Miles Lab., 997 F.2d at 876; SRI Int'l v. Matsushita Elec. Corp. of America, 775 F.2d 1107, 1121 (Fed.Cir.1985).

B. *The* "1 Patent

Enzo alleges that Calgene's FLAVR SAVR tomato literally infringes Claims 1, 3, 5, 7, 34, 66, 73 and 74 of the "1 Patent. (D.I. 525 at 164). To determine whether the Calgene FLAVR SAVR tomato infringes the Enzo "1 Patents, the Court will first construe the claims to determine their meaning, and will then compare the FLAVR SAVR tomato to the claims of the "1 Patent.

1. Claim interpretation

a. *Claim 1 of* the "1 Patent

[10] Claim 1 of the "1 Patent teaches the underlying invention of antisense common to each Enzo patent. It provides:

A prokaryotic or eukaryotic cell containing a nonnative DNA construct, which construct produces an RNA which regulates the function of a gene, said DNA construct containing the following operably linked DNA segments:

(a) A transcriptional promoter segment;

(b) A transcription termination segment;

(c) A DNA segment;

whereby transcription of the DNA segment produces a ribonucleotide sequence which does not naturally occur in the cell, is complementary to a ribonucleotide sequence transcribed from said gene, and said nonnaturally occurring ribonucleotide sequence regulates the function of said gene.

(1) A prokaryotic or eukaryotic cell... The Court concludes that the first element of claim 1 of the "1 Patent applies to both prokaryotic and eukaryotic cells by virtue of the presence of the word "or."

(2) Containing a nonnative DNA construct... The Court concludes that the prokaryotic or eukaryotic cell referred to in the first element must contain a DNA construct. This DNA construct must be comprised of a small DNA fragment or segment containing the promoter, the terminator and the genetic sequence in between as more fully described in elements (4)-(7). In addition, the Court construes the term "nonnative" to mean that the DNA construct must not occur naturally in the cell, but instead must be introduced into the cell from an outside source.

(3) Which construct produces an RNA which regulates the function of a gene... The Court concludes that the nonnative DNA construct must carry out normal cellular functions, including transcription and translation. Thus, upon transcription, the DNA construct must split its double helix, an RNA polymerase must then synthesize with one of the DNA strands according to base-pairing rules, and the RNA polymerase ultimately must produce an mRNA. Finally, the Court concludes that this non-naturally occurring mRNA must "regulate the function of a gene" by binding with a naturally-occurring mRNA from the gene targeted, and preventing the naturally-occurring mRNA from functioning.

(4) Said DNA construct containing the following operably linked DNA segments... The Court construes the term "[s]aid DNA construct" to mean the nonnative DNA construct as interpreted in element (2). The term "operably linked" means that the segments must function together as they are attached to create the DNA construct.

(5) A transcriptional promoter segment... The Court concludes that the promoter is the portion of the DNA construct which facilitates the start of the transcription of the RNA. (Green Tr. at 114). This promoter must be the starting point for the RNA polymerase to begin reading the information necessary for transcription. (Falkinham Tr. at 1413).

(6) A transcription termination segment... The Court interprets the term "transcription termination segment" to mean a configuration of bases on the fragment of the DNA construct, which must signal the end point of the RNA molecule. (Green Tr. at 114; Falkinham Tr. at 1412). Accordingly, the genetic message must "stop" at the terminator sequence or segment. (Falkinham Tr. at 1414).

(7) And therebetween, a DNA segment... The Court construes this element to require that the nonnative DNA construct must contain a DNA segment between the transcriptional promoter segment and the transcription termination segment.

(8) Whereby transcription of the DNA segment produces a ribonucleotide sequence... The Court concludes that during transcription of the nonnative DNA segment, its double helix must separate and the RNA polymerase must produce an mRNA. This mRNA must be a single stranded ribonucleotide sequence complementary to the DNA from which it was produced.

(9) Which does not naturally occur in the cell... The Court construes element (9) to require that the RNA sequence described in element (8) must result from the introduction of nonnative DNA construct into the

cell. In other words, the cell must not be able to produce the RNA sequence on its own.

(10) Is complementary to a ribonucleotide sequence transcribed from said gene... The Court concludes that the non-naturally occurring RNA sequence described in elements (8) and (9) must be complementary to a naturally occurring RNA sequence produced by the gene. However, necessary to a complete construction of this claim is the meaning of the term "complementary," which is disputed by the parties. Enzo claims that the specification of the "1 Patent defines the term "complementary" as "capable of hybridizing." For example, in column 2, lines 63-66 of the "1 Patent, it states that the DNA construct is "transcribed to produce an mRNA (micRNA) which is complementary to and capable of binding or hybridizing with the mRNA transcribed by the gene to be regulated."

[11] In interpreting a patent claim, a court generally gives the words in a claim their ordinary and customary meaning. Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1582 (Fed.Cir.1996). However, "a patentee may be his [or her] own lexicographer and use terms in a manner other than their ordinary meaning, as long as the special definition of the term is *clearly stated* in the patent specification or file history." *Id*. (citations omitted) (emphasis added). In reviewing the patent specification in this case, the Court concludes that the specification fails to clearly define the term "complementary." It is the Court's view that the use of the word "and" in the specification's references to the term "complementary" and the phrase "capable of hybridization" suggest that the specification is referring to two different characteristics of the RNA. While complementarity may be necessary for hybridization, the Court is not persuaded that the concepts are synonymous, such that one term defines the other. Accordingly, the Court rejects Enzo's contention that the patent defines the term "complementary."

[12] Because the Court concludes that the term "complementary" is not given a special meaning in the "1 Patent, the Court must turn to the ordinary and customary meaning of the term. Ordinarily defined in the context of genetic technology, the term "complementary" means "... the capacity for the *precise* pairing of ... bases between strands of DNA and sometimes RNA such that the structure of one strand determines the other." *Webster's Ninth Collegiate Dictionary* 269 (1983) (emphasis added).

Relying in part on this definition, Calgene contends that the term complementary should be narrowly construed to require complete complementarity. In response, Enzo maintains that complementary means "capable of hybridizing" and that there are no degrees or percentages of complementarity. Based on the record in this case, including the testimony of Dr. Knauf, which the Court finds credible, the Court rejects Enzo's argument and concludes that an appropriate definition of the term "complementary" requires quantification.

To the extent that Enzo's definition of complementary as "capable of hybridizing" suggests that the "1 Patent permits any degree of complementarity, the Court rejects Enzo's contention as contrary to the evidence and to existing precedent. Every example of operable antisense constructs in the specification of the "1 Patent involves a gene, or a portion of a gene, which is removed and inverted in the opposite orientation in a plasmid, and which thus, has complete complementarity with a single segment of the transcribed RNA. Indeed, because there are only four nucleotides which make up RNA, every RNA strand will have individual nucleotides and short sequences of nucleotides which are complementary to another RNA and thus, there would always be a theoretical possibility of hybridization.FN9 However, if this were the case, and the Court were to accept Enzo's contention that complementary means "capable of hybridizing," and as such, any degree of complementarity is sufficient under the "1 Patent, then the "complementary" limitation would be meaningless.

FN9. While the Court understands this to be an extreme example, it underscores the problem of accepting a definition of the term "complementary" which fails to quantify how much complementarity is required.

In addition, the Court finds this issue to be analogous to the issue before the Court of Appeals for the Federal Circuit in Genentech, Inc. v. Wellcome Found. Ltd., 29 F.3d 1555 (Fed.Cir.1994). In *Genentech,* the phrase at issue was "human tissue plasminogen activator" ("t-PA"). In interpreting this phrase, the Court rejected the broad definition sought by the patentee, which would include proteins whose amino acid sequences were not identical to natural t-PA, so long as they included important segments of the sequence or were capable of serving the same function as natural t-PA. In rejecting this broad definition, the Federal Circuit noted that the definition would cover "an infinite number of permutations," many of which would be inoperable, and that there was "no basis provided in the specification for determining which of these permutations are operative and which are not." *Id*. at 1564 (citing Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212-14 (Fed.Cir.1991)).

Similarly, in this case, the Court notes that the specification for the "1 Patent provides no guidance for determining when less than complete complementarity would make an operable antisense construct. Moreover, as discussed earlier, the specification only provides examples of operable antisense constructs that had complete complementarity with a single segment of transcribed RNA. Following the *Genentech* decision, the Court will reject the broad definition Enzo seeks, because the specification provides no basis for determining when less than complete complementarity would be successful. The Court concludes that this element of the claim requires the bases of the two RNA strands to precisely or exactly pair together according to the base pairing rules for RNA, such that complete complementarity exists between the two strands.

Also of importance to the interpretation of this claim is the meaning of the phrase "said gene" in element (10). In interpreting this language, the Court construes element (10) to require that the complementary RNA sequence must be transcribed from the gene described in element (3).

(11) Said nonnaturally occurring ribonucleotide sequence regulates the function of said gene ... The Court construes element (11) to require that the non-naturally occurring RNA sequence described in elements (8), (9), and (10) must produce an mRNA, which must be complementary to and pair with the naturally-occurring mRNA produced by RNA which is produced by the gene. The Court concludes further that this non-naturally occurring mRNA sequence must "regulate the function" of the gene by binding to the naturally-occurring mRNA and preventing it from functioning. In other words, the function of the naturally-occurring mRNA must be inhibited or disabled by the introduction of the non-naturally occurring mRNA sequence.

b. *Claim 3 of* the "1 Patent.

Claim 3 provides:

A method of regulating the function of a gene in a prokaryotic and eukaryotic cell which comprises introducing into said cell the DNA construct of claim 1.

The Court concludes that Claim 3 is a method claim, and identifies the method of regulating gene function utilizing the construct as interpreted in Claim 1. Accordingly, Claim 3 has no additional elements that the Court must interpret.

c. *Claim 5 of* the "1 Patent.

[13] Claim 5 of the "1 Patent teaches regulation of the gene function by use of an inverted gene segment. Claim 5 reads as follows:

A nonnative DNA construct which when present in a prokaryotic or eukaryotic cell containing a gene produces an RNA which regulates the function of said gene, said DNA construct containing the following operably linked DNA segments:

a. A transcriptional promoter segment;

b. A transcription termination segment;

c. A DNA segment comprising a segment of said gene, said gene segment located between said promoter segment and said termination segment and being inverted with respect to said promoter segment and said termination segment whereby the RNA produced by transcription of the inverted gene segment regulates the function of said gene.

(1) A nonnative DNA construct ... The Court concludes that interpretation of this element does not differ from element (2) of Claim 1 of the "1 Patent.

(2) Which when present in a prokaryotic or eukaryotic cell containing a gene ... The Court concludes that, like element (1) of Claim 1, this element teaches both prokaryotic and eukaryotic cells. In this element, however, the cell must contain a gene.

(3) Which regulates the function of said gene ...

(4) Said DNA construct containing the following operably linked DNA segments ...

(5) a transcriptional promoter segment ...

(6) a transcription termination segment; and ... The Court concludes that interpretation of these four elements of Claim 5 do not differ from elements (3)-(7) of Claim 1 of the "1 Patent.

(7) a DNA segment comprising a segment of said gene ... The Court construes this element to require that the nonnative DNA construct must contain a DNA segment which includes a portion of the targeted gene.

(8) Said gene segment located between said promoter segment and said termination segment ... The Court construes this element to mean that the segment of the target gene taught in element (7) must be situated between the transcriptional promoter segment and the transcription terminator segment of the DNA construct.

(9) And being inverted with respect to said promoter segment and said termination segment ... The Court concludes that this element requires an inverted gene segment, or, in other words, a "flipped" gene, or a gene that is placed in reverse orientation to the transcriptional promoter and transcription termination segments. The promoter and termination segments, however, must remain in ordinary position and order.

(10) Whereby the RNA produced by transcription of the inverted gene segment regulates the function of said gene ... The Court concludes that, like element (11) of Claim 1 of the "1 Patent, this claim teaches that the mRNA produced by transcription of the non-naturally occurring DNA must bind to the naturally-occurring mRNA, preventing the native mRNA from functioning. However, unlike element (11) of the "1 Patent, this claim requires that a flipped gene sequence described in element (9) must produce the mRNA that ultimately regulates the function of the gene.

d. ***Claim 7 of*** the "1 Patent.

Claim 7 provides:

A method of regulating the function of a gene in a prokaryotic or eukaryotic cell which comprises introducing into said cell the DNA construct of claim 5.

The Court construes Claim 7 as a method claim directed to the method of regulating gene function utilizing the construct as interpreted in Claim 5, and which needs no further interpretation.

e. *Claim 34 of* the "1 Patent.

[14] Claim 34 provides:

A nonnative nucleotide construct which, when present in a cell containing a gene, produces an RNA which regulates the function of said gene, said polynucleotide construct containing the following operatively linked polynucleotide segments:

a. a transcriptional promoter segment;

b. a transcription termination segment; and there between;

c. a polynucleotide segment;

where by transcription of a polynucleotide segment produces a ribonucleotide sequence which does not naturally occur in the cell, is complementary to a ribonucleotide sequence transcribed from said gene, and said non-naturally occurring ribonucleotide sequence regulates the function of said gene.

The Court construes the elements of Claim 34 to be no different from the elements in Claim 1 of the "1 Patent except that the fourth element of this claim teaches a "polynucleotide construct," whereas Claim 1 teaches a DNA construct.

The Court concludes that a "polynucleotide construct" is a "cellular constituent that is one of the building blocks of ribonucleic acids (RNA) and deoxyribonucleic acid (DNA). In biological systems, nucleotides are linked by enzymes in order to make long, chain like polynucleotide of defined sequence." 12 *McGraw-Hill Encyclopedia of Science and Technology* 235 (7th ed.1992). DNA is only one example of a polynucleotide construct in which nucleic acids are strung together in a certain configuration. (Green Tr. at 94; Falkinham Tr. at 1426; Shewmaker Dep. at 61). Therefore, the Court concludes that this claim teaches any polynucleotide construct, not just DNA.

f. *Claim 66 of* the "1 Patent.

Claim 66 provides:

A method of regulating a function of a gene in a cell which comprises introducing into said cell the polynucleotide construct of ... claim 34....

The Court concludes that Claim 66 is a method claim directed to the method of regulating the gene function utilizing the polynucleotide sequence as interpreted in Claim 34, and needs no further interpretation.

g. *Claim 73 of* the "1 Patent.

[15] Claim 73 provides:

A cell containing a nonnative polynucleotide construct, which construct produces an RNA which regulates the function of a gene, said polynucleotide construct containing the following operably linked polynucleotide segments:

a. a transcriptional promoter segment:

b. a transcription termination segment;

c. a polynucleotide segment comprising a segment of said gene, said gene segment located between said promoter segment and said termination segment and being inverted with respect to said promoter segment and said termination segment, whereby the RNA produced by transcription of the inverted gene segment regulates the function of said gene.

The Court concludes that the elements of Claim 73 are identical to Claim 5, except that Claim 73 teaches a nonnative polynucleotide rather than a nonnative DNA construct. As interpreted in Claim 34 of the "1 Patent, a DNA construct is an example of a polynucleotide sequence, and the Court accordingly construes this claim to be directed to all polynucleotide sequences, not just DNA.

h. ***Claim 74 of*** the "1 Patent.

Claim 74 provides:

"The cell of claim 73 wherein said cell is prokaryotic."

The Court concludes that Claim 74 is a dependent claim on Claim 73. The claim requires that the cell referred to in Claim 73 must be a prokaryotic cell, which does not contain a nucleus or a nuclear membrane.

2. Literal Infringement of Enzo' 931 Patent

[16] Having interpreted the claims of the "1 Patent, the Court will now compare the meaning of these claims to the elements found in the FLAVR SAVR tomato, as required in a literal infringement analysis.

a. ***Claim 1 of*** the "1 Patent.

(1) A prokaryotic or eukaryotic cell ... The Court finds that the FLAVR SAVR tomato contains eukaryotic cells. The Court has construed element one to teach both prokaryotic and eukaryotic cells, and accordingly, element (1) is present in the FLAVR SAVR tomato.

(2) Containing a nonnative DNA construct ... The Court finds that the FLAVR SAVR tomato utilizes an antisense construct comprised of a nonnative DNA plasmid which combines the promoter and termination segments and the genetic sequence in between. (Knauf Tr. at 1967-68). The Court has construed element (2) of the "1 Patent to require a small DNA fragment or segment that does not occur naturally in the cell, and which contains the promoter, the terminator and the genetic sequence in between. These elements are more fully discussed in elements (4)-(7). The Court finds that element (2) is present in the FLAVR SAVR tomato.

(3) Which construct produces an RNA which regulates the function of a gene ... The Court finds that once the FLAVR SAVR nonnative DNA construct, as defined in element (2), is inserted into the eukaryotic cell, it carries out normal cellular functions, such as transcription and translation. The construct produces an mRNA through transcription (Sheehy Dep. at 13-14), which is then translated to achieve polygalacturonase, or the PG enzyme. (Knauf Dep. at 151). The PG antisense construct is complementary to the PG mRNA, and shuts off the function of the PG mRNA, ultimately affecting the expression of the PG gene. (Knauf

Dep. at 152-53). The Court has construed element (3) of Claim 1 to require that the nonnative DNA construct must carry out normal cellular functions, including transcription and translation, and that the resulting non-naturally occurring mRNA must "regulate the function of a gene" by binding with a naturally-occurring mRNA from the gene targeted, and preventing the naturally-occurring mRNA from functioning. The Court finds element (3) is present in the FLAVR SAVR tomato.

(4) Said DNA construct containing the following operatively linked DNA segments ... The Court finds that the nonnative DNA construct found in the eukaryotic FLAVR SAVR tomato cell contains various DNA segments, such as a transciptional promoter segment, a transcription terminator segment and a DNA segment. These segments are more fully discussed below in the application of elements (5)-(7). Moreover, the Court finds that the segments function together as a unit to create the DNA construct.

The Court has construed the term "said DNA construct" to mean the nonnative DNA construct as interpreted in element (2), and which includes a transcriptional promoter segment, a transcription termination segment, and a DNA segment. These segments must function together as they are attached to create the DNA construct. The Court finds element (4) is present in the FLAVR SAVR tomato.

(5) A transcriptional promoter segment ... The Court finds that the Calgene antisense construct contains a transcriptional promoter segment that came from cauliflower mosaic virus, and which facilitates the start of the transcription process. (Shewmaker Dep. at 131; Hiatt Dep. at 113; Sheehy Dep. at 187).

The Court has construed element (5) of Claim 1 to require that the promoter must facilitate the start of the transcription of the RNA. Accordingly, the Court finds that element (5) is present in the FLAVR SAVR tomato.

(6) A transcription termination segment ... The Court concludes that the Calgene nonnative DNA construct contains a transcription termination segment, consisting of a series of bases which signal the end of transcription. (Shewmaker Dep. at 131; Sheehy Dep. at 187; Hiatt Dep. at 113; Knauf Dep. at 145).

The Court has construed the term "transcription termination segment" to mean a configuration of bases on the fragment of the DNA construct, which must signal the end point of the RNA molecule and the end of its genetic message. Accordingly, the Court finds that element (6) is present in the FLAVR SAVR tomato.

(7) And there between, a DNA segment ... The Court finds that a DNA segment is located between the promoter segment and the terminator segment in the Calgene DNA construct. (Shewmaker Dep. at 132; Sheehy Dep. at 187). The Court has construed element (7) to require that the nonnative DNA construct must contain a DNA segment between the transcriptional promoter segment and the transcription termination segment. Accordingly, the Court finds that finds that element (7) is present in the FLAVR SAVR tomato.

(8) Whereby transcription of the DNA segment produces a ribonucleotide sequence ... The Court finds that, after insertion of the nonnative DNA construct into the FLAVR SAVR tomato PG gene, transcription of the construct produces a ribonucleotide sequence or messenger RNA. (Sheehy Dep. at 14; Knauf Dep. 12/2/93, at 145). The Court has construed element (8) to require that transcription of the nonnative DNA segment must produce a single-stranded mRNA. Accordingly, the Court finds that element (8) is present in the FLAVR SAVR tomato.

(9) Which does not naturally occur in the cell ... The Court finds that the ribonucleotide sequence which results from transcription of the nonnative DNA construct in the Calgene FLAVR SAVR tomato would not have occurred without the introduction of the Calgene cDNA antisense construct into the cell. (Knauf Dep. at 359). The Court has construed element (9) to require that the RNA sequence described in element (8) must result from the introduction of nonnative DNA construct into the cell. Accordingly, the Court finds

that element (9) is present in the FLAVR SAVR tomato.

(10) Is complementary to ribonucleotide sequence transcribed from said gene ... The Court finds that the nonnative RNA antisense construct introduced in the FLAVR SAVR tomato is not complementary to the mRNA occurring naturally in the PG gene. The RNA produced by the Calgene cDNA structure does not include introns and, as a result, does not comport with the definition of the term "complementary" as a "precise pairing". Moreover, the Court has construed the term "complementary" to require complete complementarity. According to the testimony of Dr. Knauf, which the Court finds credible, as much as 50% of the transcribed RNA will not be complementary to the antisense RNA, because of the presence of introns in the RNA transcribed from the PG gene. (Knauf Dep. at 1911-1914). In addition, the Court finds that the RNA used by Calgene in its antisense process is not transcribed from the gene described in element (3) but is instead transcribed from a *copy* of that gene.

The Court has construed element (10) to require that the non-naturally occurring RNA sequence described in elements (8) and (9) must precisely pair with the naturally occurring RNA sequence produced by the gene described in element (3), such that complete complementarity exists between the non-naturally occurring RNA sequence and the naturally occurring RNA sequence. Based on the foregoing, the Court finds that element (10) is not present in the FLAVR SAVR tomato.

(11) Said nonnaturally occurring ribonucleotide sequence regulates the function of said gene ... The Court finds that the expression of the Calgene DNA construct regulates the expression of the PG gene in the FLAVR SAVR tomato, thus slowing down the rotting process by "block[ing] the accumulation of the polygalacturonase...." (Knauf Tr. at 1915-16; 1860-61; Hiatt Dep. at 52), and resulting in a substantial reduction in the levels of PG mRNA and enzymatic activity during fruit ripening. (PX 470 at 8805).

The Court has construed element (11) to require that the non-naturally occurring RNA sequence described in elements (8), (9), and (10) must regulate the function of the gene by binding to the naturally occurring mRNA, preventing the normal mRNA from its normal functioning. The Court finds that element (11) is present in the FLAVR SAVR tomato.

Because the Calgene FLAVR SAVR tomato does not fulfill the requirements under element (10) of Claim 1 of the "1 Patent, the Court finds that Claim 1 of Enzo's "1 Patent does not read on Calgene's FLAVR SAVR tomato product. The Court finds that the evidence presented by Enzo fails to establish by a preponderance of the evidence that all elements of Claim 1 are present in the Calgene product. Accordingly, the Court concludes that Calgene's FLAVR SAVR tomato does not infringe Claim 1 of the "1 Patent.

b. *Claim 3 of* the "1 Patent.

The Court finds that Calgene's FLAVR SAVR tomato contains a process for regulating the PG gene by introduction of a nonnative DNA construct into a eukaryotic cell, a tomato cell. (Knauf Dep. at 45, 153; Hiatt Dep. at 52; Shewmaker Dep. 128-29; Hiatt Dep. at 112-113). The Court has construed Claim 3 as a method claim which teaches gene regulation by introduction of a nonnative DNA construct, as interpreted in Claim 1, into the prokaryotic or eukaryotic cell. The Court has found that Claim 1 does not read on Calgene's FLAVR SAVR tomato. Accordingly, the Court finds that the elements of Claim 3 are not present in the FLAVR SAVR tomato. Therefore, the Court concludes that Calgene's FLAVR SAVR tomato does not infringe Claim 3 of the "1 Patent.

c. *Claim 5 of* the "1 Patent.

(1) A nonnative DNA construct ... The Court finds that this element does not differ from element (2) of Claim 1 of the "1 Patent, and that it is present in the FLAVR SAVR tomato.

(2) Which when present in a prokaryotic or eukaryotic cell containing a gene ... The Court finds that the targeted tomato cell is a eukaryotic cell containing the PG gene. The Court has concluded that, like element (1) of Claim 1, this element teaches both prokaryotic and eukaryotic cells, although in this element, the cell must contain a gene. The Court finds that element (2) is present in the FLAVR SAVR tomato.

(3) Which regulates the function of said gene ...

(4) Said DNA construct containing the following operably linked DNA segments ...

(5) a transcriptional promoter segment ...

(6) a transcription termination segment; and ... The Court has construed these four elements of Claim 5 to be identical to elements (3)-(6) of Claim 1 of the "1 Patent, and accordingly, the Court finds that each element is present in the FLAVR SAVR tomato.

(7) a DNA segment comprising a segment of said gene ... The Court finds that the antisense construct used in the FLAVR SAVR tomato does not utilize a PG gene, but rather a copy DNA ("cDNA"), in which the cDNA synthesizes a strand of DNA from a gene's strand of RNA. (Knauf Tr. at 1911; Green Tr. at 131).

The Court has construed this element to require that the nonnative DNA construct must contain a DNA segment which contains a segment of the targeted gene. Because the Court finds that Calgene did not use a gene *per se* but instead used a copy of the gene's DNA, the Court finds that element (7) is not present in the FLAVR SAVR tomato.

(8) Said gene segment located between said promoter segment and said termination segment ... In element (7) of Claim 1, the Court found that the Calgene product contained a DNA segment between the promoter and termination segments. However, in element (7) of this Claim, the Court has found that the Calgene DNA construct does not use a gene segment, but rather a copy of the DNA. Since the Court has construed this element to require that the gene taught in element (7) must be situated between the promoter segment and the terminator segment of the DNA construct, and the DNA construct does not contain this gene, but rather a copy of the DNA of the gene, the Court finds that element (8) is not present in the FLAVR SAVR tomato.

(9) And being inverted with respect to said promoter segment and said termination segment ... The Court has found that the DNA segment used by Calgene is not the PG "gene," but rather a copy of the DNA of the gene. The Court additionally finds that the cDNA is not flipped with respect to the promoter and termination segments of the DNA construct.

The Court has construed this element to require an inverted gene segment, or, in other words, a "flipped" gene, or a gene that is placed in reverse orientation to the promoter and termination segments, which remain in ordinary position and order. Because the Calgene DNA segment is not an inverted gene, the Court finds element (9) is not present in the FLAVR SAVR tomato.

(10) Whereby the RNA produced by transcription of the inverted gene segment regulates the function of said gene ... The Court has already found in element (11) of Claim 1 of the "1 Patent that the construct used by Calgene regulates the function of the PG gene. The Court has also found in elements (7) and (9) of Claim 5 that cDNA is not an inverted gene segment.

The Court has concluded that, like element (11) of Claim 1 of the "1 Patent, this claim teaches that the mRNA produced by transcription of the non-naturally occurring DNA must bind to the naturally-occurring

mRNA, preventing the native mRNA from functioning. However, unlike element (11) of Claim 1 of the "1 Patent, this Claim requires that the flipped gene sequence described in element (9) must produce the mRNA that ultimately regulates the function of the gene. Because a flipped gene sequence did not create the mRNA in the Calgene antisense construct, the Court finds that element (10) is not present in the FLAVR SAVR tomato.

Because Enzo has failed to establish that elements (7), (8), (9) and (10) of Claim 5 read on the Calgene FLAVR SAVR tomato, the Court concludes that Claim 5 of the "1 Patent is not infringed by Calgene's FLAVR SAVR tomato.

d. ***Claim 7 of*** the "1 Patent.

The Court finds that the FLAVR SAVR tomato includes a method for regulating a gene by introducing a DNA construct in an inverted position into a eukaryotic cell by an agrobacterium vector. (Shewmaker Dep. at 128-29; Hiatt Dep. at 112-113; Knauf Dep. at 45).

The Court has construed Claim 7 as a method claim directed to the method of regulating gene function utilizing the construct as interpreted in Claim 5 into the prokaryotic or eukaryotic cell. Since the Court has found that all the elements of Claim 5 of the "1 Patent do not read on the Calgene antisense construct, the Court finds that the methods are different, and therefore, that the elementsof Claim 7 are not present in the FLAVR SAVR tomato. Accordingly, the Court concludes that the FLAVR SAVR tomato does not infringe Claim 7 of the "1 Patent.

e. ***Claim 34 of*** the "1 Patent

The Court has construed Claim 34 to be identical to Claim 1 of the "1 Patent, except that Claim 34 teaches "nonnative polynucleotide constructs" rather than "nonnative DNA constructs," and that Claim 34 accordingly teaches any polynucleotide construct, not just DNA. The Court finds that the Calgene DNA construct is an example of a polynucleotide construct. However, the Court has determined that element (10) of Claim 1 of the "1 Patent does not read on the FLAVR SAVR tomato. Because the Court has found that Claim 1 does not read on Calgene's FLAVR SAVR tomato, the Court finds the elements of Claim 34 are also not present in the FLAVR SAVR tomato. Accordingly, the Court concludes that Claim 34 of the "1 Patent is not infringed by the FLAVR SAVR tomato.

f. ***Claim 66 of*** the "1 Patent.

The Court finds that the FLAVR SAVR utilizes an agrobacterium vector method to introduce the polynucleotide construct into the cell. (Shewmaker Dep. 128-29; Hiatt Dep. at 112-113; Knauf Dep. 9/1/93, at 45).

The Court has construed Claim 66 as a method claim teaching regulation of the function of a gene by introducing into a cell the polynucleotide construct claimed in Claim 34. Because the Court has found that the elements of Claim 34 are not present in the FLAVR SAVR tomato, the Court finds that the elements of Claim 66 are not present in the FLAVR SAVR tomato. Accordingly, the Court concludes that Claim 66 of the "1 Patent is not infringed by the FLAVR SAVR tomato.

g. ***Claim 73 of*** the "1 Patent

The Court has construed Claim 73 to teach the same elements as Claim 5, except that Claim 73 teaches a nonnative polynucleotide gene segment in lieu of the DNA segment. The Court has found in Claim 34 that the DNA construct used by Calgene is an example of a polynucleotide construct. In addition, the Court has also determined that the elements of Claim 5 are not present in the FLAVR SAVR tomato. Because the

Court has determined that the elements of Claim 5 are not present in the FLAVR SAVR tomato, the Court finds that the elements of Claim 73 are also not present in the FLAVR SAVR tomato. Accordingly, the Court concludes that Claim 73 of the "1 Patent is not infringed by the FLAVR SAVR tomato.

h. *Claim 74 of* the "1 Patent

The Court finds that the FLAVR SAVR tomato contains eukaryotic, not prokaryotic, cells. The Court has construed Claim 74 to require that the cell discussed in Claim 73 be prokaryotic. Because the FLAVR SAVR tomato is not prokaryotic, the Court finds that the elements of Claim 74 are not present in the FLAVR SAVR tomato. Accordingly, the Court concludes that Claim 74 of the "1 Patent is not infringed by Calgene's FLAVR SAVR tomato.

In sum, the Court concludes that Enzo has failed to meet its burden of proving by a preponderance of the evidence that the Calgene FLAVR SAVR tomato literally infringes Enzo's "1 Patent.

3. Doctrine of Equivalents Infringement

A device or product may infringe a patent even where the patent is not literally infringed, as long as the accused product performs substantially the same function in substantially the same way to achieve substantially the same result. *See* section III. A., *supra*.

[17] In its literal infringement analysis, the Court found that Enzo has not established, by a preponderance of the evidence, that the claims of its "1 Patent read on the Calgene FLAVR SAVR tomato antisense process. In order to prove infringement under the doctrine of equivalents, Enzo must demonstrate that the Calgene antisense process performs substantially the same function in substantially the same way to achieve substantially the same result as does the antisense method in the "1 Patent.

The Court concludes that the Calgene antisense process is a different method than the antisense process under the "1 Patent, and accordingly fails to meet the standard for a finding of infringement under the doctrine of equivalents. The Calgene antisense process utilizes cDNA, which is a copy of the RNA in DNA form. While the effect of cDNA is exactly the same as the use of the inverted gene in that it regulates the function of the naturally occurring mRNA, essentially shutting off the function of the PG gene, there is no question that the method of inserting a flipped gene is far different than the method of inserting a copy of a gene.

Moreover, Enzo has failed to establish that the prokaryotic cell taught in Claim 74 reads on the Calgene FLAVR SAVR tomato. The FLAVR SAVR tomato utilizes a eukaryotic cell, not a prokaryotic cell. Accordingly, Enzo's infringement challenge again fails on the grounds that its method, utilizing a prokaryotic cell, is far different than Calgene's method, which uses a eukaryotic cell.

Accordingly, because Enzo has failed to establish that the Calgene antisense process performs substantially in the same way as the antisense process in the "1 Patent, the Court concludes that Calgene has not infringed the "1 Patent under the doctrine of equivalents.

C. *The* '149 Patent

Enzo claims that Calgene literally infringes Claim 1, Claim 31, Claim 61, Claim 93, Claim 125 and Claim 159 of the '149 Patent. (D.I. 363; D.I. 525 at 164). Calgene denies that its FLAVR SAVR tomato infringes the '149 Patent. (D.I. 367; D.I. 518 at pp. 200-203). As with the "1 Patent, the Court will first construe the claims to identify their meaning, and will then compare them with the Calgene FLAVR SAVR tomato to determine whether the Calgene FLAVR SAVR tomato infringes the '149 Patent. After reviewing the testimony and exhibits, the Court concludes that Enzo has failed to establish that the FLAVR SAVR tomato

contains every element of the Enzo '149 Patent, and accordingly, has failed to establish that the Calgene FLAVR SAVR tomato literally infringes the '149 Patent. The Court concludes that Enzo has failed to establish that the Calgene process provides a substantially similar method to the '149 Patent, and accordingly concludes that Enzo has failed to establish infringement of the '149 Patent under the doctrine of equivalents.

1. Claim Interpretation

a. ***Claim 1 of*** the '149 Patent.

[18] Claim 1 of the '149 Patent provides:

A nonnative polynucleotide construct comprising:

a. a transcriptional promoter segment;

b. a segment coding for a stable stem and loop structure with a negative AG of formation operably linked downstream of said promoter segment; and

c. a polynucleotide segment comprising a gene segment operably linked downstream of said promoter segment and inverted with respect to a gene in a cell, whereby the transcript of said inverted gene segment regulates the function of said gene.

(1) A nonnative polynucleotide construct comprising ... The Court construes the term "polynucleotide construct" to mean any string of nucleotides, including DNA, as discussed in Claim 34 of the "1 Patent. "Nonnative" means something not originating in the cell, but instead introduced from an outside source.

(2) A transcriptional promoter segment ... The Court concludes that "a transcriptional promoter segment" is the same as in element (5) of Claim 1 of the "1 Patent, and means the portion of the construct which facilitates the start of transcription.

(3) A segment coding for a stable stem and loop structure with a negative [delta]>G of formation operatively linked down stream of said promoter segment ... The Court interprets the phrase "stem and loop structure" to mean a single strand of nucleic acid that folds back onto itself and then hybridizes by forming and collapsing. The Court construes the phrase "negative [delta]>of formation" to mean that the stem and loop structure requires a negative measurement of [delta] to insure that the stem and loop structure is stable. (Simmons Tr. at 1708-10; D.I. 518 at 193-94). To be "operably linked," the nucleic acid segments must function together as they are attached to create the stem and loop construct. Finally, the Court concludes that this Claim requires that the stem and loop segment must be linked downstream of the transcriptional promoter segment identified in element (2).

(4) A polynucleotide segment comprising a gene segment ... The Court concludes that this element requires that the polynucleotide segment must make up a part of a gene.

(5) Operably linked downstream of said promoter segment ... The Court concludes that the polynucleotide segment from element (4) must be located downstream of the promoter segment identified in element (2).

(6) And inverted with respect to a gene in a cell ... The Court concludes that the polynucleotide construct described in element (4) must be inverted with respect to a certain gene in a certain cell. This means that the orientation of the bases in the construct must be flipped or reversed with regard to the orientation of the bases in the gene.

(7) Whereby the transcript of said inverted gene segment regulates the function of said gene ... The Court construes this element to require that, upon introduction into the cell, the inverted gene segment described in element (6) must undergo transcription and produce an mRNA. This mRNA must be complementary to and pair with the naturally-occurring mRNA produced by the gene. The Court concludes further that the inverted gene must be able to "regulate the function" of the target gene by pairing with the naturally-occurring mRNA, and preventing it from functioning.

b. Claim 31 of the '149 Patent**.**

[19] Claim 31 of the '149 Patent provides:

A nonnative polynucleotide construct which produces in a cell, a nonnaturally occurring polynucleotide complementary to a RNA transcript produced by a gene in said cell, said nonnaturally occurring polynucleotide further comprising a stable stem and loop structure with a negative [delta] of formation, whereby said nonnaturally occurring polynucleotide regulates the function of said gene in said cell.

(1) A nonnative polynucleotide construct ... The Court concludes that "a nonnative polynucleotide construct" has the same meaning as in Claim 1.

(2) Which produces in a cell, a nonnaturally occurring polynucleotide ... The Court concludes that the nonnative polynucleotide construct must produce, through transcription, a nonnaturally occurring polynucleotide, and it must produce it in a cell.

(3) Complementary to a RNA transcript produced by a gene in said cell ... The Court concludes that the polynucleotide described in element (1), created through transcription of the nonnative construct, must be complementary to the mRNA transcript that is produced from the "native" gene in the cell. The Court concludes that the term "complementary" has the same meaning as the Court concluded in its discussion of Claim 1 of the "1 Patent.

(4) Said nonnaturally occurring polynucleotide further comprising a stable stem and loop structure with a negative [delta] of formation ... The Court concludes that the non-naturally occurring polynucleotide must also have a stable stem and loop structure evidenced by a negative [delta] of formation, as described more fully in element (3) of Claim 1.

(5) Whereby said nonnaturally occurring polynucleotide regulates the function of said gene in said cell ... The Court concludes that the nonnaturally occurring polynucleotide must regulate the function of the targeted gene, discussed in element (3), in the targeted cell, discussed in element (2). As interpreted above in element (7) of Claim 1, the Court construes the phrase "regulates the function" to mean that the nonnative polynucleotide is transcribed and translated so as to alter the gene's normal function.

c. *Claim 61 of* the '149 Patent.

[20] Claim 61 of the '149 Patent provides:

A cell comprising a nonnative polynucleotide construct comprising:

a. a transcriptional promoter segment;

b. a segment coding for a stable stem and loop structure with a negative [delta] of formation operably linked downstream said promoter segment; and

c. a polynucleotide segment comprising a gene segment operably linked downstream of said promoter segment and inverted with respect to a gene in a cell, whereby the transcript of said inverted gene segment-regulates the function of said gene.

The Court concludes that Claim 61 is identical to Claim 1 with one exception. The Court construes Claim 61 to teach a cell that includes the polynucleotide construct, whereas Claim 1 does not teach a cell. All other elements are interpreted as in the Court's Claim 1 interpretation.

d. *Claim 93 of* the '149 Patent.

[21] Claim 93 of the '149 Patent provides:

A cell comprising a nonnative polynucleotide construct which construct produces in said cell a nonnaturally occurring polynucleotide complementary to an RNA transcript produced by a gene in said cell, said non-naturally occurring polynucleotide further comprising a stable stem and loop structure with a negative [delta] of formation, whereby said nonnaturally occurring polynucleotide regulates the function of said gene in said cell.

The Court concludes that Claim 93 is identical to Claim 31, with one exception. The Court construes Claim 93 to teach a cell that includes the polynucleotide construct, whereas Claim 31 does not teach a cell. All other elements are interpreted as in the Court's Claim 31 interpretation.

e. *Claim 125 of* the '149 Patent.

[22] Claim 125 of the '149 Patent provides:

A method of regulating the function of a gene in a cell, comprising the steps of:

(a) preparing a nonnative polynucleotide construct which comprises

(i) a transcriptional promoter segment;

(ii) a segment coding for a stable stem and loop structure with a negative [delta]>of formation operably linked downstream of said promoter segment; and

(iii) a polynucleotide segment comprising a gene segment operably linked downstream of said promoter segment and inverted with respect to a gene in a cell; and

(b) introducing said nonnative polynucleotide construct into said cell containing said gene; whereby the transcript of said inverted gene segment regulates the function of said gene.

The Court concludes that Claim 125 is a method claim. The elements of Claim 125 include all elements, as interpreted, in Claim 1. However, the Court construes Claim 125 to also teach the method of introducing the nonnative polynucleotide construct into the cell in which the gene regulation is desired.

f. Claim 159 of the '149 Patent**.**

[23] Claim 159 reads as follows:

A method of regulating the function of a gene in a cell, comprising introducing into a cell a nonnative polynucleotide construct which, produces a nonnaturally polynucleotide complementary to an RNA

transcript produced by said gene in said cell, said nonnaturally occurring polynucleotide further comprising a stable stem and loop structure with a negative [delta] of formation, whereby said nonnaturally occurring polynucleotide regulates the function of said gene in said cell.

The Court concludes that Claim 159 is a method claim. The elements of Claim 159 contain all the elements, as interpreted, in Claim 31. However, the Court construes Claim 159 to also teach the method of regulating gene function by introducing into a cell the nonnative polynucleotide construct as defined and interpreted in Claim 31.

2. Literal Infringement of the '149 Patent

a. ***Claim 1 of*** the '149 Patent

[24] **(1) A nonnative polynucleotide construct comprising ...** The Court found in its analysis of Claim 34 of the "1 Patent that the FLAVR SAVR tomato contains a nonnative polynucleotide construct. The Court has concluded that "a nonnative polynucleotide construct" has the same meaning as in Claim 34 of the "1 Patent. Therefore, further analysis of this element is unnecessary.

(2) A transcriptional promoter segment ... The Court found in its analysis of Claim 1 of the "1 Patent that the antisense construct in the FLAVR SAVR tomato contains a transcriptional promoter segment. The Court has concluded that "a transcriptional promoter segment" has the same meaning as in Claim 1 of the "1 Patent. Therefore, further analysis of this element is unnecessary.

(3) A segment coding for a stable stem and loop structure with a negative [delta]>of formation operably linked downstream of said promoter segment ... The Court finds that the Calgene FLAVR SAVR tomato does not specifically rely on a stable stem and loop construct for its antisense regulation. (Simmons Tr. at 1719-20; D.I. 518 at 203-04). The Court has concluded that element (3) requires the presence of a stem and loop structure in the form of a single strand of nucleic acid that folds back upon itself and hybridizes. Because the Calgene construct does not require a stem and loop construct to function, the Court finds that element (3) is not present in the FLAVR SAVR tomato.

(4) A polynucleotide segment comprising a gene segment ... The Court finds that the FLAVR SAVR tomato contains a polynucleotide segment that is made up of a copy of a segment of the PG gene. (Shewmaker Dep. at 131-32). The Court has construed this element to require that the polynucleotide segment must make up a part of a gene. Accordingly, the Court finds that element (4) is present in the FLAVR SAVR tomato.

(5) Operably linked downstream of said promoter segment ...

The Court finds that the polynucleotide sequence utilized in the FLAVR SAVR tomato is located downstream from the promoter segment. The Court has construed this element to require that the polynucleotide segment which contains the gene segment must be located downstream of the promoter segment identified in element (2). Accordingly, the Court finds that element (5) is present in the FLAVR SAVR tomato.

(6) Inverted with respect to a gene in a cell ... The Court found in element (9) of Claim 5 of the "1 Patent that the antisense construct which utilizes cDNA in the FLAVR SAVR tomato is not inverted with respect to the PG gene. The Court has construed element (6) of the '149 Patent to require that the construct be inverted with regard to a gene in the cell. Accordingly, the Court finds that element (6) is not present in the FLAVR SAVR tomato.

(7) Whereby the transcript of said inverted gene segment regulates the function of said gene ... The Court has found in element (11) of Claim 1 of the "1 Patent that the antisense construct utilized in Calgene's FLAVR SAVR tomato does regulate the function of the PG gene. However, in element (6) of this Claim, the Court has also found that the cDNA utilized in the Calgene antisense construct is not inverted. The Court has construed this Claim to require that an inverted gene must undergo transcription and translation to regulate the function of the target gene. Because the Calgene construct does not utilize an inverted gene, the Court finds element (7) is not present in the FLAVR SAVR tomato.

Because Enzo has failed to establish that the construct used by Calgene uses a stem and loop construct as required by element (3), or that it uses an inverted gene as required by elements (6) and (7), the Court finds that Enzo has failed to demonstrate that all the elements of Claim 1 of the '149 Patent are present in the FLAVR SAVR tomato. Accordingly, the Court concludes that Claim 1 of the '149 Patent is not infringed by Calgene's FLAVR SAVR tomato.

b. *Claim 31 of* the '149 Patent.

(1) A nonnative polynucleotide construct ... The Court found in its analysis of Claim 1 of the '149 Patent that the FLAVR SAVR tomato contains a nonnative polynucleotide construct. The Court has concluded that "a nonnative polynucleotide construct" has the same meaning as in Claim 1. Therefore, no further analysis of this element is required here.

(2) which produces in a cell, a nonnaturally occurring polynucleotide ... The Court finds that introduction of the Calgene antisense construct produces a polynucleotide in the form of an mRNA which would not otherwise occur, and which the construct produces while in the eukaryotic tomato cell. (Sheehy Tr. at 13-14). The Court has concluded that the nonnative polynucleotide construct must produce, through transcription, a nonnaturally occurring polynucleotide. Accordingly, the Court finds that element (2) of Claim 31 is present in the FLAVR SAVR tomato.

(3) complementary to a RNA transcript produced by a gene in said cell ... The Court found in Claim 1 of the '149 Patent that the FLAVR SAVR tomato utilizes a polynucleotide. The Court also found in Claim 1 of the "1 Patent that the nonnaturally occurring RNA antisense construct in the FLAVR SAVR tomato is not complementary to an RNA transcript produced by the PG gene in the tomato cell. (Knauf Dep. at 364-65; Sheehy Dep. at 17). The Court has construed element (3) to require that the polynucleotide created through transcription of the nonnative construct must be complementary to the mRNA transcript that is produced from the "native" gene in the cell. Accordingly, the Court finds that element (3) of Claim 31 is not present in the FLAVR SAVR tomato.

(4) said nonnaturally occurring polynucleotide further comprising a stable stem and loop structure with a negative [delta] of formation ... In element (3) of Claim 1 of the '149 Patent, the Court determined that the Calgene antisense construct does not consist of a stem and loop structure. The Court concluded that the non-naturally occurring polynucleotide must have a stable stem and loop structure. Accordingly, the Court finds that element (4) of Claim 31 is not present in the FLAVR SAVR tomato.

(5) Whereby said nonnaturally occurring polynucleotide regulates the function of said gene in said cell ... In element (11) of Claim 1 of the "1 Patent, the Court found that the nonnative construct introduced into the tomato cell of the FLAVR SAVR tomato regulates the function of the PG gene in the tomato cell. The Court concluded that the nonnaturally occurring polynucleotide must regulate the function of the specific gene. Accordingly, the Court finds that element (5) of Claim 31 is present in the FLAVR SAVR tomato.

Because Enzo has failed to establish that the construct used by Calgene uses a stem and loop construct as

required by element (4), and because Enzo has failed to establish that the cDNA used by Calgene in its antisense is complementary to the RNA produced by the gene as required by element (3), the Court finds that Enzo has failed to demonstrate that all elements of Claim 31 of Enzo's '149 Patent are present in Calgene's FLAVR SAVR tomato. Accordingly, the Court concludes that Claim 31 of the '149 Patent is not infringed by the FLAVR SAVR tomato.

c. *Claim 61 of* the '149 Patent.

The Court has construed Claim 61 of the '149 Patent to require the same elements as Claim 1 of the '149 Patent, with the additional element that Claim 61 teaches that a cell must comprise the polynucleotide construct. Because the elements of Claim 1 of the '149 Patent have not been met, the Court finds that the elements of Claim 61 are not present in the FLAVR SAVR tomato. Accordingly, the Court concludes that Claim 61 of the '149 Patent is not infringed by the FLAVR SAVR tomato.

d. *Claim 93 of* the '149 Patent.

The Court has construed Claim 93 to require the same elements as Claim 31, with the additional element that Claim 31 teaches that a cell must comprise the nonnative polynucleotide construct. Because the elements of Claim 31 are not present in Calgene's FLAVR SAVR tomato, the Court concludes that the elements of Claim 93 are not present in the FLAVR SAVR tomato. Accordingly, the Court concludes that Claim 93 of the '149 Patent is not infringed by Calgene's FLAVR SAVR tomato.

e. *Claim 125 of* the '149 Patent.

The Court has construed Claim 125 as a method claim which includes all the elements of Claim 1 of the '149 Patent, but which also teaches the method of introducing the nonnative polynucleotide construct into the cell in which the gene regulation is desired. However, because the FLAVR SAVR tomato does not contain all the elements of Claim 1 of the '149 Patent, the Court finds that the elements of Claim 125 are not present in the FLAVR SAVR tomato. Accordingly, the Court concludes that Claim 125 of the '149 Patent is not infringed by the FLAVR SAVR tomato.

f. *Claim 159 of* the '149 Patent.

The Court has construed Claim 159 as a method claim which teaches the method of regulating gene function by introducing into a cell the nonnative polynucleotide construct described in Claim 31. Because the Court has found that the Calgene antisense construct does not contain the elements of Claim 31, the Court finds that the elements of Claim 159 are not present in the FLAVR SAVR tomato. Accordingly, the Court concludes that Claim 159 of the '149 Patent is not infringed by the FLAVR SAVR tomato.

Because Enzo has not established that the Calgene construct meets all of the elements under any of the claims that it has alleged that Calgene infringes, the Court concludes that Enzo has failed to meet its burden of establishing that the Calgene FLAVR SAVR tomato literally infringes Enzo's '149 Patent. The Calgene FLAVR SAVR tomato does not utilize a stem and loop construct as required in element (3) of Claim 1 and element (4) of Claim 31, an inverted gene as required in element (6) of Claim 1 or a complementary sequence as required by element (3) of Claim 1. The infringement of Claims 61, 93, 125 and 159 are each in some way dependant on the infringement of Claims 1 or 31. Accordingly, the Court concludes that the Calgene FLAVR SAVR tomato does not literally infringe Enzo's '149 Patent.

3. Infringement of the '149 Patent **under Doctrine of Equivalents**

[25] As discussed in Section III.A., *supra,* a patent may be infringed even where its elements have not been literally infringed as long as the accused device performs substantially the same function in substantially the

same way to achieve substantially the same result. *See* Section III.A., *supra*. Applying the doctrine of equivalents analysis, the Court finds that the Calgene antisense process does not perform essentially the same function in the same manner as the method patented in Enzo's '149 Patent.

Enzo has also failed to establish by a preponderance of the evidence that the Calgene process utilizes a method that performs in substantially the same way as the stem and loop construct taught by Claim 1. Despite the fact that the cDNA ultimately achieves substantially the same result as the stem and loop process, it does not do so in a manner similar to the stem and loop process. Therefore, the Court concludes that the Calgene FLAVR SAVR tomato does not infringe Enzo's '149 Patent under the doctrine of equivalents.

D. ***Conclusion***

Because Enzo has failed to establish that the Calgene FLAVR SAVR tomato contains every element of at least one claim of the "1 or '149 Patents, the Court concludes that Calgene's FLAVR SAVR tomato does not literally infringe the "1 or '149 Patents. In addition, because Enzo has failed to establish that the Calgene FLAVR SAVR tomato performs substantially the same function in substantially the same way to achieve substantially the same result, the Court concludes that the FLAVR SAVR tomato does not infringe the "1 or the '149 Patents under the doctrine of equivalents.

IV. INVALIDITY OF ENZO PATENTS

In its counterclaims, Calgene contends that the "1 and '149 Patents are invalid and unenforceable due to non-enablement, anticipation, obviousness from prior art references, and inequitable conduct before the PTO. The Court will now turn its attention to Calgene's counterclaims.

A. ***Enablement under*** 35 U.S.C. s. 112

Neither Enzo nor Calgene distinguish the claims of the patents in suit on a claim-by-claim analysis. Because the specifications of the patents claim application of the inventions to all cells in all organisms, the Court will not evaluate enablement on a claim-by-claim basis. The Court understands, however, that the principal claim at issue in the enablement challenge asserted by Calgene is Claim 1 of the "1 Patent. Accordingly, the Court's decision concerns Claim 1 of the "1 Patent unless otherwise stated, however, the Court's conclusions necessarily apply to all claims at issue.

[26] [27] Patents are presumed valid unless proved otherwise. 35 U.S.C. s. 282; Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc., 796 F.2d 443, 446 (Fed.Cir.1986), *cert. denied,* 484 U.S. 823, 108 S.Ct. 85, 98 L.Ed.2d 47 (1987). Invalidity must be proven by clear and convincing evidence by the party claiming the invalidity. Bausch & Lomb, 796 F.2d at 446, *citing Loctite,* 781 F.2d at 872. Patentability depends upon satisfaction of all three elements: novelty, utility and non-obviousness. United States v. Adams, 383 U.S. 39, 48-52, 86 S.Ct. 708, 15 L.Ed.2d 572 (1966); Structural Rubber Prod. Co. v. Park Rubber Co., 749 F.2d 707, 714 (Fed.Cir.1984). In this case, then, if any one of these element is not satisfied, the patents must be declared invalid.

1. Arguments of the Parties

Calgene alleges that the Enzo "1 and '149 Patent specifications do not enable one of ordinary skill in the art to make and use the patented invention in all genes in all organisms. Calgene argues that not one of the three examples of artificial antisense presented in Enzo's patent specification contains examples of antisense regulation in genes other than those found in the prokaryotic organism *E. coli*. (D.I. 520 at 23). Moreover, Calgene contends that at the time Dr. Inouye filed his patent applications, he could not successfully demonstrate applicability to eukaryotic cells, and, in fact, sought grants to study whether antisense

regulation could be successful in eukaryotes. (D.I. 520 at 24). Calgene asserts that practice of the Enzo's patents beyond the three examples presented in them requires undue experimentation by individuals with extraordinary skill in the art. (D.I. 520 at 28).

Enzo responds that Calgene has failed to meet its burden of proof to demonstrate invalidity of the "1 and '149 Patents. (D.I. 525 at 35). Enzo argues that Dr. Inouye's findings based on the model system *E. coli,* a prokaryote, apply to eukaryotes as well. At trial and in its post-trial briefs, Enzo argued that the patent does not have to identify all promoters that would be required to practice the invention in different organisms, but instead has to provide a method by which "[m]ost promoters and terminators would in fact be discovered and invented in the future as the targets [are] discovered and sequenced." (D.I. 525 at 39).

2. Establishing an Enablement Claim

The enablement standard is set forth at 35 U.S.C. s. 112. Section 112 provides:

[t]he 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 which 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.

Id.

[28] For a specification to be valid, it must (1) enable a person skilled in the art to use the invention as broadly as it is claimed (2) without undue experimentation. 35 U.S.C. 112; In re Goodman, 11 F.3d 1046, 1050 (Fed.Cir.1993). Finally, it must do so from the time the patent specification is filed. *Id.*

[29] [30] Patent claims may still be enabled, however, even if some experimentation is necessary to practice the claims. In re Wands, 858 F.2d 731, 736-37 (Fed.Cir.1988). The specification need not provide "every conceivable and possible future embodiment of [the] invention." SRI Int'l. v. Matsushita Elec. Corp. of America, 775 F.2d 1107, 1121 (Fed.Cir.1985). Greater disclosure is required, however, where the unpredictability of the relevant art increases. *Application of Fisher,* 57 C.C.P.A. 1099, 427 F.2d 833, 839 (Cust.&Pat.App.1970).

[31] Undue experimentation is determined by evaluating the following factors:

(1) the quantity of experimentation necessary;

(2) the amount of direction or guidance presented in the specification;

(3) the presence or absence of working examples;

(4) the nature of the invention;

(5) the state of the prior art;

(6) the relative skill of those in the art;

(7) the predictability or unpredictability of the art; and,

(8) the breadth of the claims at issue.

In re Wands, 858 F.2d at 737.

[32] [33] [34] Under the second prong of the enablement analysis, the Court must also assess the level of those skilled in the art. Relevant factors in this regard include the various prior art approaches employed; educational level of the inventor; problems encountered in the art; sophistication of the technology; and education of others, including witnesses, working in the field. Orthopedic Equipment Co., Inc. v. United States, 702 F.2d 1005, 1011 (Fed.Cir.1983). The skill of the inventor should not be considered as the level of ordinary skill. Standard Oil Co. v. American Cyanamid Co., 774 F.2d 448, 454 (Fed.Cir.1985). "A person of ordinary skill is one who thinks along the line of conventional wisdom in the art and is not one who undertakes to innovate ...." *Id*.

3. Enablement of "1 and '149 Patents

a. ***Level of Ordinary Skill in the Art***

[35] Both parties presented witnesses at trial concerning the level of ordinary skill in the art. Calgene proposes that an individual of ordinary skill in the art pertinent to the claimed invention would be a junior faculty member in molecular biology with one or two years experience or a postdoctoral scientist with several years of experience in the laboratory. (Falkinham Tr. at 1525; Simons Tr. at 1667).

Enzo proposes that a high level of ordinary skill in the art is required due to the cutting edge nature of the biotechnology utilized in the claimed inventions. Thus, Enzo contends that a person of ordinary skill in the art could range between the postdoctoral student with a few years of lab experience and the Nobel laureate. (D.I. 525 at 72). Furthermore, Enzo stresses that application of a "team concept" of enablement is appropriate in this case. (D.I. 525 at 73). Enzo argues that the *field* of skill, in this case, a highly specialized field, is important in this determination. Enzo asserts that where technology is very complex, one person will rarely practice an invention outside of his or her specialty. (D.I. 525 at 73). Thus, Enzo proposes that the team concept would have the effect of pooling knowledge from various disciplines and various individuals. (D.I. 525 at 74).

After considering the evidence offered by the parties, the Court is persuaded that a person with ordinary skill in the art would be a junior faculty member with one or two years of relevant experience or a postdoctoral student with several years of experience. The Court bases its conclusion largely on the background of the witnesses who testified at trial. These witnesses conducted most of the research and experiments of the antisense technology, usually working alone, and with academic and work experience in line with the standard adopted by the Court.

b. ***Undue Experimentation***

After a review of the evidence presented at trial under the factors set forth in *Wands,* the Court concludes that undue experimentation is necessary to achieve antisense in cells other than the ones specifically described in the patent specifications of the "1 and '149 Patents.

The evidence establishes that the quantity of experimentation required to achieve the invention in cells other than ompA, ompC and lpp is quite high. For example, Dr. Inouye never successfully practiced antisense in any other genes in *E. coli,* and never in eukaryotic cells. Even the reports of a possible recent success of Dr. Inouye's invention regulating the mouse hepatitis virus gene fail to salvage Dr. Inouye's invention from the enablement graveyard, because enablement must be determined from the time the specification was filed. At the relevant time, Dr. Inouye had trouble applying his antisense principles to regulate the expression of other genes, and acknowledged that eukaryotic cells had not yet been so regulated. In further support of the Court's non-enablement conclusion, the record is unchallenged that after Dr. Inouye filed his original application for the "1 Patent, he sought over $700,000 from the National Institute of Health to study whether

the mic antisense system could work in eukaryotic cells, acknowledging in the grant application that "the micRNA regulatory system *may* be a general regulatory phenomenon in *E. coli* and other organisms including eukaryotic cells." (DX 69 (Inouye Grant Application) at 24 (emphasis added)).

Additionally, other scientists had similar trouble achieving Dr. Inouye's antisense system in eukaryotic cells. (*See* Wold Dep. at 84 (work in Thymidine kinase); Crowley Dep. at 54-55 (work in Dictyostelium discoideum-slime mold); Davis Dep. at 25-30 (work in saccharomyces-baker's yeast)). One witness, Dr. Wold, published an article stating that eukaryotic cells have "posttranscriptional aberrant processing," a process not found in prokaryotic cells. (Wold Dep. at 33-35). According to Dr. Wold, the existence of this process could explain the failure to accumulate sufficient quantities of antisense RNA to successfully regulate expression of a gene. (Wold Dep. at 49-51). Only experimentation with other genes on a case-by-case basis would resolve whether this process would interfere with the success of the regulation. (Wold Dep. at 50-51).

The Court concludes that the Enzo patents fail to meet the next two *Wands* factors as well. First, the direction or guidance presented in the specifications of the '1 and '149 Patents relies on the working examples included in the specification: the prokaryotic *E. coli* genes ompA, ompC, and lpp. Second, the Inouye patents do not contain working examples for eukaryotic cells, and, therefore, the scope of direction or guidance, as well as the variety of examples, is very narrow.

The Enzo patents also fail to meet the "predictability of the art" factor. Witnesses testified at trial and in depositions that antisense is highly unpredictable. (*See* Inouye Tr. 466-469; Firtel Dep. at 7-8 ("it is a little bit of witchcraft in the sense that sometimes it's just not clear why something might not work"); Melton Dep. at 67-68; Davis Dep. at 45; Wold Dep. at 53-54). Dr. Inouye himself agreed that genetic antisense experiments are trial and error types of experiments. (Inouye Tr. 469-70). Based on this record, the Court concludes that the predictability of the art is highly uncertain.

The final *Wands* factor, the breadth of the claims at issue, is critical to the enablement analysis. Under this factor, the Court must determine whether the claims are enabled as broadly as the specifications claim. The Federal Circuit has generally held that patent specifications claiming enablement broader than their underlying examples are not enabled. For example, in *In re Goodman,* the Federal Circuit found that claims that taught "gene transformation for use with monocot plants" were not enabled, because the application of the process needed extensive experimentation for the few plants claimed in the application, and accordingly provided too broadly that the claimed method was applicable to all plants. In re Goodman, 11 F.3d at 1052. In addition, in *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.,* the Federal Circuit emphasized that where an invention claims every possible outcome, but discloses only an invention and very few examples, the patent is not enabled. Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd., 927 F.2d 1200, 1214 (Fed.Cir.), *cert. denied sub nom.* Genetics Inst., Inc. v. Amgen, Inc., 502 U.S. 856, 112 S.Ct. 169, 116 L.Ed.2d 132 (1991).

Like the inventions at issue in *Goodman* and *Amgen,* the '1 and '149 Patents claim broad applicability. The '1 Patent teaches antisense in all prokaryotic and eukaryotic cells. The '149 Patent, an improvement patent over the '1 Patent, claims applicability to "cells." In essence, these patents attempt to include the entire universe of cells for the antisense system detailed.

Following the teachings of *Goodman* and *Amgen,* the Court concludes that the claims of the Inouye patents boast greater success than they were capable of achieving at the time the patent applications were filed. The record evidence clearly demonstrates that Dr. Inouye's invention was successful for only three genes in *E. coli* cells. There is no credible evidence that success was achievable in eukaryotic cells, as claimed in the patents. Thus, the Court concludes that the claims of applicability to both prokaryotic and eukaryotic cells were too broad at the time the patent application was filed and are simply not supported by the evidence.FN10

FN10. Although Enzo contends that success has *since* been reported in eukaryotes, as stated previously the claims had to be enabled at the time the application was filed. For example, Calgene's expert Dr. Robert Simons acknowledged at trial that he was familiar with approximately 20 cases of successful antisense gene regulation in eukaryotes. (Simons Tr. at 1820). Additionally, Dr. Falkinham, another Calgene witness, testified that he was aware of approximately 20-30 successful cases of antisense in plants and mammals. (Falkinham Tr. at 1580). Successful application of antisense, however, has taken extensive experimentation often by those individuals who exemplify extraordinary skill in the art.

Although Enzo repeatedly characterizes Dr. Inouye's invention as a basic principle or theory which requires further experimentation for applicability in different genes, *Goodman* and *Amgen* stand for the proposition that theory alone is an insufficient basis to meet the enablement standard. Although the Court agrees with Enzo that failure is routine in science and that failure of an experiment should not mean that the theory or principle is faulty, (*see* D.I. 525 at 26), the lack of success in the specific genes that the patent claims to teach requires a nonenablement conclusion by the Court.

Accordingly, the Court concludes that Calgene has proven by clear and convincing evidence that undue experimentation was necessary to practice the "1 Patent and the '149 Patent, and therefore the patents are not enabled and must be declared invalid and unenforceable. Because the Court has found that the patents are not enabled, it need not reach the issues of anticipation and obviousness concerning those patents, since the validity of a patent requires a finding that the patent is enabled.FN11

FN11. Since the Court has determined that the patents are invalid because they are not enabled, the Court also does not reach the issue of whether the patents are invalid as a result of Enzo and Dr. Inouye's alleged inequitable conduct before the PTO.

V. INVALIDITY OF CALGENE'S '065 PATENT

A. *Arguments of the Parties*

Enzo seeks a declaratory judgment that Calgene's '065 Patent is invalid because it was made obvious by the work and publications of Dr. Inouye and others.FN12 (D.I. 525 at 9). Enzo argues that Dr. Inouye invented the "universally applicable concept of antisense," and that Calgene copied the concept of antisense from Dr. Inouye's work, rendering the Calgene patent invalid on obviousness grounds. (D.I. 525 at 9, 186). Enzo contends it has standing to seek a declaratory judgment on the invalidity of Calgene's '065 Patent, because Calgene's '065 Patent interferes with Enzo's ability to market licenses under its own antisense patents. (D.I. 525 at 180).

FN12. Enzo apparently has retreated from its initial argument that the Dr. Inouye's work anticipated the Calgene patent, as it presented no evidence to that effect at trial, nor did it brief the issue in its post-trial briefs, although it does mention it in its Introduction. (*See also* D.I. 520 at 103 (Calgene pointing out that Enzo presented no evidence on this issue)). Therefore, the Court will only address the obviousness issue.

In response, Calgene contends that the Court does not have subject matter jurisdiction over Enzo's declaratory judgment claim, and that Enzo failed to produce testimony or evidence at trial to establish that there was subject matter jurisdiction. (D.I. 520 at 101, 103). Second, Calgene argues that even if the Court has jurisdiction, Enzo has failed to meet its burden of establishing invalidity by clear and convincing evidence, as it failed to present any evidence at the trial to prove the invalidity of the Calgene '065 Patent.

(D.I. 520 at 103).

B. ***Legal Standard***

[36] [37] Where an invention is not anticipated by 35 U.S.C. s. 102, a patent nonetheless should not issue if the differences between the claimed invention and the prior art are such that the invention as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. 35 U.S.C. s. 103. If no single prior art reference anticipates each and every claim, but a combination thereof possibly does, the proper inquiry is obviousness, not lack of novelty. Messerschmidt v. United States, 29 Fed.Cl. 1, 21 (1993), *aff'd,* 14 F.3d 613 (Fed.Cir.1993), *cert. denied,* 511 U.S. 1010, 114 S.Ct. 1382, 128 L.Ed.2d 57 (1994) (citing Connell v. Sears, Roebuck & Co., 722 F.2d 1542, 1548 (Fed.Cir.1983)). Like enablement and anticipation, the defense of obviousness must be proved by clear and convincing evidence. Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc., 796 F.2d 443, 446 (Fed.Cir.1986), *cert. denied,* 484 U.S. 823, 108 S.Ct. 85, 98 L.Ed.2d 47 (1987).

[38] Under section 103, the question of obviousness is determined by (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the pertinent art; and (4) secondary objective considerations such as commercial success, long felt but unsolved needs, failure of others, copying of the invention, taking of licenses or praise by others in the field. Graham v. John Deere Co., 383 U.S. 1, 17-18, 86 S.Ct. 684, 15 L.Ed.2d 545 (1966); Orthopedic Equip. Co., Inc. v. All Orthopedic Appliances, Inc., 707 F.2d 1376, 1379 (Fed.Cir.1983); *see also* Pentec, Inc. v. Graphic Controls Corp., 776 F.2d 309, 316 (Fed.Cir.1985) (discussing objective factors). References relied on for obviousness must enable a person of ordinary skill, not of the skill of the inventor, to duplicate the process so that the invention is in the possession of the public. Phillips Petroleum Co. v. United States Steel Corp., 673 F.Supp. 1278, 1316 (D.Del.1987), *aff'd,* 865 F.2d 1247 (Fed.Cir.1989).

C. ***Discussion***

[39] Assuming that Enzo does have standing to assert a claim for declaratory judgment, after a review of the record evidence, the Court concludes that Enzo has failed to meet its burden of establishing the invalidity of Calgene's '065 Patent by clear and convincing evidence, either through testimony or exhibits admitted at trial. Enzo produced two witnesses who testified that the Calgene '065 Patent is invalid on obviousness grounds, but both concluded that Dr. Inouye's work did not make antisense obvious in plants. (D.I. 518 at 590; Borogard Tr. at 1996; Knauf Tr. at 1954). Moreover, examination of Dr. Inouye's publications admitted at trial also fails to convince the Court that the Calgene '065 Patent should be declared invalid.

Under the *Graham* test for obviousness discussed above, the Court finds that the Calgene invention differs from the prior art of Dr. Inouye's invention in that Calgene's invention involves antisense in eukaryotic cells. Dr. Inouye's invention, while it suggested the applicability of antisense to eukaryotic cells, did not teach how Dr. Inouye's antisense system could regulate the expression of eukaryotic genes, as discussed previously in Section IV.A., *supra*. Also, Calgene invested millions of dollars in research and development in its efforts to successfully regulate gene expression in eukaryotic cells, which the Court finds persuasive and supportive of its conclusion that Dr. Inouye's antisense system did not render antisense in eukaryotic cells obvious. Finally, the Court finds the fact that three licenses have been taken under the Calgene '065 Patent as strong evidence of the rejection of obviousness under the fourth prong of *Graham*.

Accordingly, the Court concludes that Enzo has failed to establish by clear and convincing evidence that Calgene's '065 Patent is invalid on the ground of obviousness.

VI. ENZO'S MALICIOUS PROSECUTION CLAIM

A. ***Arguments of the Parties***

Enzo asserts that Calgene's lawsuit against Enzo in California was a "textbook case of malicious prosecution." (D.I. 525 at 10, 209). Enzo argues that Calgene brought suit in California to inconvenience Enzo, and to stave off litigation by Enzo. (D.I. 525 at 220, 221). Calgene answers that Enzo has failed to establish two elements necessary to maintain a malicious prosecution claim. Specifically, Calgene contends that Enzo has not established or offered any credible evidence that Calgene commenced its lawsuit against Enzo either (1) with malice or (2) without probable cause.

B. *Legal Standard*

[40] The parties agree that California law governs this issue. Under California law, a plaintiff seeking damages for malicious prosecution must show that the prior action (1) was commenced by or at the direction of the defendant and pursued to legal termination favorable to the plaintiff; (2) was brought without probable cause; and (3) was initiated with malice. Pender v. Radin, 23 Cal.App.4th 1807, 1813-14, 29 Cal.Rptr.2d 36 (1994), *citing* Sheldon Appel Co. v. Albert & Oliker, 47 Cal.3d 863, 872-73, 254 Cal.Rptr. 336, 765 P.2d 498 (1989); *see also* Bertero v. National General Corp., 13 Cal.3d 43, 50, 118 Cal.Rptr. 184, 529 P.2d 608 (1974).

[41] [42] To show probable cause, the action must only be "legally tenable" or "arguably correct even if it is extremely unlikely to win." Leonardini v. Shell Oil Co., 216 Cal.App.3d 547, 568, 264 Cal.Rptr. 883 (1989), *cert. denied,* 498 U.S. 919, 111 S.Ct. 293, 112 L.Ed.2d 247 (1990). Malice means "actual ill will or some improper purpose, whether express or implied." Grindle v. Lorbeer, 196 Cal.App.3d 1461, 1465, 242 Cal.Rptr. 562 (1987).

C. *Discussion*

[43] After a review of the record evidence, the Court is persuaded that Enzo has not established a claim for malicious prosecution. While Defendant Calgene did commence the prior action in California, and pursued it to legal termination favorable to Enzo, Enzo has failed to show that Calgene acted without probable cause and with malice. Enzo's allegation that Calgene brought suit in California to inconvenience Enzo does not rise to malice, as the plaintiff in a lawsuit may bring its suit in any forum in which the defendant can be sued.

In addition, the Court finds that Enzo has failed to establish that Calgene lacked probable cause when commenced its lawsuit. Calgene has offered evidence that Enzo's actions, including its press releases, caused actual disruption to Calgene's public offering. This evidence is in the form of expert testimony and exhibits regarding the actual drop in the price of Calgene's stock. Accordingly, the Court concludes that Enzo has failed to carry its burden on two of the elements required to make out a prima facie case of malicious prosecution on the part of Calgene.

VII. ATTORNEY'S FEES

Calgene claims that Enzo's behavior before the PTO and this Court renders this an exceptional case under 35 U.S.C. s. 285, thus entitling Calgene to an award of attorney's fees. (D.I. 520 at 112). Calgene argues that Enzo engaged in inequitable conduct before the PTO, withheld vital documents in this litigation until the Court ordered Enzo to produce the documents, filed frivolous motions claiming Calgene engaged in criminal activity which were denied by the Court, and asserted numerous non-patent claims, such as fraud and deceit, which Enzo dismissed after substantial discovery had taken place. (D.I. 520 at 112-116). Enzo also claims that this is an exceptional case, and also asks for attorney's fees. (D.I. 525 at 10, 209, 221).

In the present litigation climate, the Court is unable to conclude that the conduct of either party supports a finding of "exceptional circumstances". The Court views the conduct and tactics of the parties as within the

standard of conduct prevalent in patent litigation today, and, therefore, the Court concludes that the litigation conduct of the parties does not warrant an award of attorney's fees.

VIII. CONCLUSION

For the reasons discussed, the Court concludes that Enzo's "1 and '149 Patents are not infringed by Calgene's FLAVR SAVR tomato. The Court also concludes that Enzo's "1 and '149 Patents are not enabled, and therefore are invalid.

Further, the Court concludes that Calgene's '065 Patent is valid and not obvious, and that Calgene's lawsuit against Enzo in California was not malicious.

Finally, the Court concludes that this case is not an exceptional case under the standard of 35 U.S.C. s. 285, and accordingly will not award attorney's fees to either party.

A Final Judgment Order consistent with this Opinion will be entered.