IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

CANCER RESEARCH TECHNOLOGY, et al.,	)	
Plaintiffs,	)	
v.	)	Civ. No. 07-457-SLR
BARR LABORATORIES, INC., et al.,	)	
Defendants.	)	

Jack B. Blumenfeld, Esquire and Rodger D. Smith II, Esquire of Morris, Nichols, Arsht & Tunnell LLP, Wilmington, Delaware. Counsel for Plaintiffs. Of Counsel: Jesse J. Jenner, Esquire, Denise L. Loring, Esquire, Christopher J. Harnett, Esquire and Matthew A. Traupman, Esquire of Ropes & Gray LLP, New York, New York.

John C. Phillips, Esquire and Brian E. Farnan, Esquire of Phillips, Goldman & Spence, P.A., Wilmington, Delaware. Counsel for Defendants. Of Counsel: George C. Lombardi, Esquire, Lynn M. Ulrich, Esquire, Ivan M. Poullaos, Esquire, and Julia M. Johnson, Esquire of Winston & Strawn LLP, Chicago, Illinois.

OPINION

Dated: January 26, 2010
Wilmington, Delaware

ROBINSON, District Judge

I. INTRODUCTION

This action arises out of the filing of an Abbreviated New Drug Application ("ANDA")[1] by Barr Laboratories, Inc. and Barr Pharmaceuticals, Inc. (collectively, "Barr")[2] in 2007 for a generic version of the brain cancer drug Temodar® (temozolomide[3]). Plaintiff Cancer Research Technology Limited[4] ("CRT") is the assignee of U.S. Patent No. 5,260,291 ("the '291 patent"), claiming tetrazine derivative compounds and methods of treating various cancers using tetrazine derivative compounds. Plaintiff Schering Corporation ("Schering") is the exclusive licensee of the '291 patent. Schering is the holder of an approved New Drug Application[5] for the manufacture and sale of temozolomide for the treatment of two types of brain cancers: glioblastoma multiforme and refractory anaplastic astrocytoma. (D.I. 1 at ¶ 15) In response to Barr's ANDA filing, on July 20, 2007, plaintiffs brought a patent infringement suit pursuant to 35 U.S.C. § 271(e)(2)(A).[6] (D.I. 1) Plaintiffs' suit triggered

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[1]No. 78-879.

[2]Barr Laboratories, Inc. is a wholly-owned subsidiary of Barr Pharmaceuticals, Inc. (D.I. 8 at ¶ 6) The court notes Barr Phamaceuticals, Inc.'s defense that is not a proper party to this action. (*Id.* at 2, n.1; *id.* at 5) For simplicity, and without passing judgment on the issue, the court refers to "Barr" as one entity.

[3]A tetrazine derivative (8-Carbamoyl-3-methylimidazo(5,1-d)-1,2,3,5-tetrazin-4(3H)-one) of the formula $C_6H_6N_6O_2$.

[4]Formerly Cancer Research Campaign Technology Limited, as discussed *supra* in the opinion. (D.I. 1 at ¶ 2)

[5]No. 21-029.

[6]"(2) It shall be an act of infringement to submit – (A) an application under section 505(j) of the Federal Food, Drug, and Cosmetic Act or described in section

the 30-month stay on the FDA's approval of Barr's ANDA for its generic temozolomide capsules.[7] *See* 21 U.S.C. § 355(j)(5)(B)(iii). Barr concedes infringement of claims 1, 3, 5-7, 11-13 and 27 of the '291 patent. (D.I. 72) A bench trial was held between March 30, 2009 and April 2, 2009 on two unenforceability defenses raised by Barr: prosecution laches and inequitable conduct. These issues were fully briefed post-trial. The court has jurisdiction pursuant to 28 U.S.C. §§ 1331, 1338(a) and 1400(b). Having considered the documentary evidence and testimony, the court makes the following findings of fact and conclusions of law pursuant to Fed.R.Civ.P. 52(a).

II. FINDINGS OF FACT AND CONCLUSIONS OF LAW

A. Background

1. The parties and the technology at issue

1. Schering is a New Jersey corporation with its principal place of business in Kenilworth, New Jersey. Barr Laboratories, Inc. and Barr Pharmaceuticals, Inc. are Delaware corporations with principal operations in Pomona, New York. Schering and Barr are pharmaceutical drug companies involved in the manufacture of chemotherapy drugs.

2. CRT is a limited liability company organized and existing under the laws of the United Kingdom and having its principal place of business in London. CRT is a wholly owned subsidiary of Cancer Research UK, the world's largest independent funder of cancer research. CRT is a charity that works with scientists to facilitate the

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505(b)(2) of such Act for a drug claimed in a patent or the use of which is claimed in a patent[.]"

[7]Barr represents that the stay expires on or about January 27, 2010.

identification and development of new cancer drugs and therapies. Temozolomide is licensed by CRT to Schering. CRT utilizes royalties from these and other technologies to fund further research projects.

2. The '291 patent[8]

3. The '291 patent, entitled "Tetrazine Derivatives," contains 33 claims: 26 to tetrazine derivatives (claims 1-26); one to a pharmaceutical composition (claim 27); and six directed to methods for the treatment of a patient (claims 28-31) and the treatment of specific cancers (claims 32-33).

4. The '291 patent specification provides "new therapeutically useful compounds possessing antineoplastic activity." ('291 patent, Abstract) More specifically, the patent provides that

> [t]he new tetrazine derivatives of general formula I possess valuable antineoplastic activity, for example against carcinomas, melanomas, sarcomas, lymphomas and leukemias. They possess useful activity against glioma and mycosis fungoides. They have proved **particularly active** in mice at daily doses between 0.5 and 16 mg/kg animal body weight, administered intraperitoneally, **against TLX5 (S) lymphomas** according to the procedure of Gescher et al, Biochem. Pharmacol. (1981), 30, 89, and ADJ/PC6A and M5076 (reticulum cell sarcoma). **Against leukemia L1210**, grafted intraperitoneally, intracerebrally and intravenously, and P388, according to the procedure described in "Methods of Development of New Anticancer Drugs" (NCI Monograph 45, March 1977, pages 147-149, National Cancer Institute, Bethesda, United States), the compounds were **active** both intraperitoneally and orally at doses of between 2.5 and 10 mg/kg animal body weight. Inhibition of both primary tumor and metastasis was obtained against the Lewis lung carcinoma by similar dosage regimes. Against the B16 melanoma and C38 tumour in mice (NCI Monograph 45, op cit.) the compounds were active intraperitoneally at doses of between 6.25 and 25 mg/kg animal body weight.

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[8]The parties do not dispute the essential facts regarding the '291 patent and its prosecution history. The court adopts in large part Barr's statement of facts in this regard. (D.I. 194)

> The tetrazine derivatives also possess valuable immunomodulatory activity and are of use in the treatment of organ grafts and skin grafts and in the treatment of immunological diseases.

(*Id.*, col. 4, ll. 29-56) (emphasis added) The specification proceeds to identify thirteen "**[i]mportant** individual compounds of general formula I," labeled as compounds A through M.[9] (*Id.*, col. 4, l. 59 – col. 5, l. 16) (emphasis added) According to the patent, "[c]ompounds A and D, and especially C, are of **particular importance**." (*Id.*, col. 5, ll. 17-18) (emphasis added) Compound A is temozolomide (the active ingredient in Temodar®); compound C is mitozolomide (the first compound tested by the applicants in animals and humans); and compound D is a mitozolomide-related compound (a mitozolomide with a methyl group on the carbonyl ring). (D.I. 188 at 178:15; D.I. 189 at 445:13-21) Each compound is individually claimed.

5. Claim 1 is the only independent compound claim, and reads as follows:

> A [3H]-imidazo[5,1-d]-1,2,3,5-tetrazin-4-one derivative of the formula:

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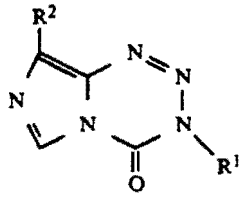
[9]8-carbamoyl-3-methyl-[3H]-imidazo[5,1-d]-1,2,3,5-tetrazin-4-one [compound "A"];
8-carbamoyl-3-n-propyl-[3H]-imidazo[5,1-d]-1,2,3,5-tetrazin-4-one [compound "B"];
8-carbamoyl-3-(2-chloroethyl)-[3H]-imidazo-[5,1-d]-1,2,3,5-tetrazin-4-one [compound "C"]; 3-(2-chloroethyl)-8-methylcarbamoyl-[3H]-imidazo[5,1-d]-1,2,3,5-tetrazin-4- one [compound "D"];
8-carbamoyl-3-(3-chloropropyl)-[3H]-imidazo-[5,1-d]-1,2,3,5-tetrazin-4-one [compound "E"]; 8-carbamoyl-3-(2,3-dichloropropyl)-[3H]-imidazo[5,1-d]-1,2,3,5-tetrazin-4-one [compound "F"]; 3-allyl-8-carbamoyl-[3H]-imidazo[5,1-d]-1,2,3,5-tetrazin-4-one [compound "G"];
3-(2-chloroethyl)-8-dimethylcarbamoyl-[3H]-imidazo[5,1-dl-1,2,3,5-tetrazin- 4-one [compound "H"];
3-(2-bromoethyl)-8-carbamoyl-[3H]-imidazo-5,1-d]-1,2,3,5-tetrazin-4-one [compound "I"]; 3-benzyl-8-carbamoyl-[3H]-imidazo[5,1-d]-1,2,3,5-tetrazin-4-one [compound "J"];
8-carbamoyl-3-(2-methoxyethyl)-[3H]-imidazo[5,1-d]-1,2,3,5-tetrazin-4-one [compound "K"]; 8-carbamoyl-3-cyclohexyl-[3H]-imidazo[5,1-d]-1,2,3,5-tetrazin-4-one [compound "L"]; and 8-carbamoyl-3-(Wmethoxybenzyl)-[3H]imidazo[5,1-d]-1,2,3,5-tetrazin-4-one [compound "M"].



wherein R^1 represents hydrogen, or an alkyl, alkenyl or alkynyl group containing from 1 to 6 carbon atoms, or a said group substituted by from one to three substituents selected from halogen atoms, alkoxy, alkylthio, alkylsulphinyl and alkylsulphonyl groups containing up to 4 carbon atoms, and phenyl substituted by alkoxy and alkyl groups containing from 1 to 4 carbon atoms or a nitro group; or R^1 represents a cycloalkyl group containing from 3 to 8 carbon atoms, and R^2 represents a carbamoyl group, or a carbamoyl group carrying on the nitrogen atom one or two groups selected from alkyl and alkenyl groups containing up to 4 carbon atoms, and cycloalkyl groups containing from 3 to 8 carbon atoms, and--when R^1 represents hydrogen--alkali metal salts thereof.

6. Barr focused on claim 13 at trial,[10] which reads:

> A tetrazine derivative according to claim 1 which is 8-carbamoyl-3-methyl-[3H]-imidazo[5,1-d]-1,2,3,5-tetrazin-4-one.

In other words, claim 13 recites temozolomide.

7. The '291 patent lists five inventors: Edward Lunt ("Lunt"), Malcolm F. G. Stevens ("Stevens"), Robert Stone ("Stone"), Kenneth R. H. Woolridge ("Woolridge"), and Edward S. Newlands ("Newlands"). Stevens and Stone are medicinal chemists who developed tetrazine derivatives beginning in 1980 pursuant to a collaborative agreement between Aston University ("Aston") in England and May & Baker ("M&B"), a U.K.-based pharmaceutical company. (PTX-200) Stevens was a professor of experimental cancer chemotherapy at Aston University; Stone was an Aston University

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[10]Barr asserts that each claim is relevant under the equitable doctrines asserted in its defense.

Ph.D. candidate. (D.I. 188 at 133:2-10) Lunt and Wooldridge were employees of M&B who were involved in the preclinical testing of a number of the tertazine derivatives. Newlands was added to the application in 1993 based on his work on the clinical testing of temozolomide in glioma. (PTX-2 at A220-27 & A236) In connection with the patent application, each inventor signed a Declaration acknowledging their duty to disclose material information to the Patent and Trademark Office ("PTO"). (PTX-3 at A474-75)

3. Prosecutorial timeline and relevant events

8. The first application in the series leading to the '291 patent, U.S. Patent Application No. 06/410,656 ("the '656 application"), was filed August 23, 1982 – one year after the filing of British Patent Application No. 8125791 on August 24, 1981. (PTX-3 at A477) M&B's British patent counsel was Stephen Bentham ("Bentham") of the firm J.A. Kemp & Co.

9. The '291 patent, which issued November 9, 1993, claims priority to the filing of the '656 application through a chain of continuation applications as described below.[11] The '291 patent expires in February 2014,[12] almost thirty-two years after the first application in this chain was filed. All together, the prosecution of the '291 patent involved eleven patent applications and ten abandonments.

10. Terry Miller ("Miller"), a patent manager at M&B, was responsible for the prosecution of the '656 application and subsequent applications from August 1982 until

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[11]The 29 as-filed claims of the '656 application mirror the issued claims 1-29 of the '291 patent. (PTX-3 at A465-72)

[12]The '291 patent was granted a patent term extension and pediatric exclusivity period.

approximately March 1991. (D.I. 190 at 609:19-23) The '656 application was filed August 23, 1982 by U.S. patent attorney Ellsworth Mosher ("Mosher"). Examiner John M. Ford was assigned the '656 application.

11. An office action was mailed in the '656 application on November 18, 1983.[13] Examiner Ford issued a utility rejection based on the "Medical Use" provision formerly found at MPEP 608.01(p). The MPEP stated as follows:

> Proof of utility under this section [608.01(p)] may be established by clinical or in vivo or in vitro data, or combinations of these, which would be convincing to those skilled in the art. . . . More particularly, if the utility relied on is directed solely to the treatment of humans, evidence of utility, if required, must generally be clinical evidence, (Ex parte Timmis, 123 U.S.P.Q. 581) although animal tests may be adequate where the art would accept these as appropriately correlated with human utility. . . . or where animal tests are coupled with other evidence, including clinical evidence and a structural similarity to compounds marketed commercially for the same indicated uses[.][14]

12. Examiner Ford explained the rejection as follows.

> Statements of utility which relate to or simply imply the treatment of a disease are subject to closer scrutiny. . . Thus, when the disclosed utility is the production of a physicological response, e.g., antidepressant effect, the dosage effective to achieve this response, whether human or animal, must be disclosed. . . .
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> * * *
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> The District Court for the District of Columbia held the patent office should be careful and perhaps even reluctant to grant a patent on a medicinal composition until it has been thoroughly tested and tried by several physicians, on the theory that some members of the public would rely on the "official imprimatur" given to the medicin[e] by the granting of a patent thereon. *Issenstead v. Watson*,

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[13]At oral argument, defendants highlight this action as "exemplary of all the remaining office actions in the case."

[14]It does not appear that either party admitted the relevant MPEP at trial. At the post-trial oral argument, the parties provided the May 1988 revision (Rev. 8) to the 5th Edition of the MPEP (1983). The court relies on the parties' iteration of the relevant guideline.

(DCDC 1957) F. Supp. 7, 115 U.S.P.Q. 408[.]

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> The treatment of leukemia is not a believable utility on its face. . . . The [B]oard of Appeals and the CCPA have held that even though the specification does not mention human use specifically, the Patent Office is not precluded from finding an inference of human use and require proof thereof, when such use is of a medical nature [ ] for the treatment of serious disease, such as cancer. *Ex parte Moore et al.*, (POBA 1960) 128 U.S.P.Q. 8; *In re Citron*, (CCPA 1964) 325 F.2d 248, 139 U.S.P.Q. 516; *In re Hartop et al.*, (CCPA 1962) 311 F.2d 249, 135 U.S.P.Q. 419.
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> Remission of a specific leukemia could be establish[ed], but has not been so accomplished here or so claimed.

(PTX-3 at A500-502)

13. No response was filed to the November 18, 1983 office action in the '656 application. U.S. Patent Application No. 06/586,635 ("the '635 application"), a continuation of the '656 application, was then filed by the applicants on March 6, 1984; the '656 application was subsequently abandoned. (PTX-3 at A503)

14. An office action was issued in the '635 application in October 1984.[15] (*Id.* at A512) Examiner Ford was assigned the '635 application, and repeated his arguments made in rejection of the claims in the '656 application.

15. No response was filed. U.S. Patent Application No. 06/712,462 ("the '462 application"), a continuation of the '635 application, was filed by the applicants on March 15, 1985; the '635 application was subsequently abandoned. (*Id.* at A519)

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[15]The '635 application contained 31 claims. (PTX-3 at A512) The Examiner noted that restriction was required in the '656 application to one utility to be examined with the compound claims. The applicants elected the method use with respect to the treatment of leukemia. That election carried into the '635 application and, as part of his first office action, the examiner required the applicants to cancel or amend claims 27-30 to read solely on the elected use. (*Id.*)

16. Examiner Ford was assigned the '462 application and, on June 17, 1985, he issued an office action in the '462 application mirroring that filed in the '656 application. (*Id.* at A525) No response was filed. U.S. Patent Application No. 06/798,365 ("the '365 application"), a continuation of the '462 application, was filed by the applicants on November 18, 1985; the '462 application was subsequently abandoned. (*Id.* at A533)

17. An office action rejecting the '365 application was issued by Examiner Ford on January 24, 1986. (PTX-3 at A540) No response was filed. Rather, the applicants filed a continuation application, U.S. Patent Application No. 06/885,397 ("the '397 application") on July 18, 1986, and abandoned the '365 application. Examiner Ford was assigned the '397 application and issued a rejection on October 21, 1986. (*Id.* at A549)

18. In lieu of a response, applicants filed U.S. Patent Application No. 07/040,716 ("the '716 application"), another continuation application, on April 20, 1987. (*Id.* at A558) Examiner Ford issued a rejection on August 19, 1987. (*Id.* at A564)

19. U.S. Patent Application No. 07/135,473 ("the '473 application"), a continuation application, was filed on December 21, 1987. (*Id.* at A576) The '716 application was subsequently abandoned. Examiner Ford was assigned the '473 application and issued a rejection on October 4, 1988, reiterating that "[t]he treatment of leukemia is not a believable utility on its face," and issuing a best mode rejection stating the following:

> Claim 1 is rejected under 35 U.S.C. [§]112. In the definition of R1, note "optionally substituted phenyl." What is the phenyl "optionally substituted" with? No actual best mode of using the compounds is seen in pages 29-31 of the specification. **There is still a best mode requirement. . . . No in vivo or in**

vitro tests are noted. No tests in laboratory animals are noted.

> *Brenner v. Manson*, 148 U.S.P.Q. 689, requires more than a laboratory curiosity. The compounds need to be related to the practical world of commerce. Repeated disclosure of how to make a solution for parenteral administration or a capsule does not disclose the best mode intended for how to **use** the instant compounds for a specific purpose, among the many alleged.

(PTX-3 at A583-84) (first emphasis added) Applicants did not respond. U.S. Patent Application No. 07/338,515 ("the '515 application") was filed on March 3, 1989 as a continuation application, and the '473 application was abandoned. (*Id.* at A587)

20. The '515 application was examined by Examiner Johann Richter, a supervisory patent examiner in Examiner Ford's art unit. (PTX-3 at A595) On June 30, 1989, Examiner Richter issued an office action rejecting the claims on utility, enablement, and best mode grounds; the action was made final. With respect to utility, Examiner Richter repeated Examiner Ford's reasoning that the treatment of leukemia or cancer is not believable on its face. (*Id.* at A591) Examiner Richter also reiterated that the Board has held that "even though the specification does not mention human use specifically, the [PTO] is not precluded from finding an inference of human use and require proof thereof, when such use is of a medical nature for the treatment of a serious disease, such as cancer." (*Id.*)

21. Again, applicants filed a continuation application in lieu of a response. U.S. Patent Application No. 07/456,614 ("the '614 application") was filed December 29, 1989, and the '515 application was abandoned.[16]

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[16]On December 29, 1989, the applicants filed a Revocation and Power of Attorney with the PTO, naming several Morgan & Finnegan attorneys as attorneys of record in the '614 application in place of Mosher. (PTX-3 at A617)

22. Examiner Richter issued a rejection in the '614 application on May 1, 1990, wherein he repeated his utility and 35 U.S.C. § 112 rejections. (*Id.* at A607[17]) No response was filed. On November 1, 1990, Mr. Calavetti of Morgan & Finnegan filed on behalf of the applicants a continuation application, U.S. Patent Application No. 07/607,221 ("the '221 application"). (*Id.* at A627) The '614 application was abandoned.

23. U.S. Patent Application No. 07/781,020 ("the '020 application") was filed as a continuation-in-part from the '221 application on October 18, 1991. The '020 application ultimately matured into the '291 patent.

24. On October 18, 1991, Attorney Rzucidlo of Morgan & Finnegan filed a Preliminary Amendment and Remarks with the '020 application addressing the utility rejection, stating:

> It is believed that this rejection should be reconsidered in view of the disclosure of other utilities for the present compounds as well as the disclosure at page 8 and 9, connecting paragraph **wherein the effectiveness of the present compounds is demonstrated.**

(PTX-2 at A63) (emphasis added)

4. Licensing activities and the '020 application

25. Prior to 1991, M&B had a "strategy review, as a result of which they had decided that their interest in oncology generally was low and also that mitozolomide [compound C] was not a favorable candidate." (D.I. 191 at 769:11-14) M&B decided not to pursue studies with mitozolomide due to the toxic side effects seen in the phase I trials. (*Id.* at 768:3-17)

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[17]Although the preceding office action was a final rejection, neither this action nor subsequent office actions were made final.

26. By this time, Stevens, Newlands, and other colleagues in this field had obtained positive results with temozolomide. In March 1989, the "Sixth NCI-EORTC symposium on new drugs and cancer therapy" was held in Amsterdam. (DTX-574) An abstract from that conference, entitled "Phase I trial of temozolomide,"[18] is informative on the state of the art at that time.

> A number of 3-alkyl analogs of the experimental antitumour drug mitozolomide have been screened against murine tumors in vivo. Only the compounds with a 3-methyl- or 3-bromoethyl group possessed significant antitumor [effects] against the TLX5 lymphoma. The 3-methyl analogue, 8-carbamoyl-3-methylimidazo[5,1-d]-1,2,3,5-tetrazin-4(3H)-one (temozolomide) was investigated further and found to possess good activity when administered i.p. against the L1210 and P388 leukemias, the M5076 reticulum cell sarcoma, B126 melanoma and ADJ/PC6A plasmacytoma. The drug was also active when administered p.o. to mice bearing the L1210 leukemia. . . Mitozolomide underwent phase II testing in Europe but its development has been stopped owing to unpredictable and prolonged thrombocytopaenia. Temozolomide was chosen for development since it is thought to spontaneously activate to MTIC which is a potent alkylating agent[.]
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> * * *
>
> Two clinical improvements were observed [with temozolomide]: one in a patient with malignant melanoma and the other had squamous cell carcinoma of the head and neck but neither was a partial response.

(*Id.*) (*See also* PTX-67 at 187 ("temozolomide showed broad spectrum activity" and "increased therapeutic activity against both P388 and L1210 leukemias") (1990); PTX-68 at 773 (Phase I testing of temozolomide revealed "clinical activity . . . in two patients with melanoma (1 CR at 10+ months and 1 PR at 7+ months) and a complete response in mycosis fungoides lasting 3+ months") (1990))

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[18]By Newlands and R. Hoffman of Charing Cross Hospital in London, U.K., J. Slack, C. Quartermain and Stevens of Aston University, and Blackledge and N. Stuart of Queen Elizabeth Hospital in Birmingham, U.K.

27. Despite M&B's decision not to pursue mitozolomide, Stevens wanted the work on tetrazine derivatives to continue. Stevens spoke with Dr. Sue Foden ("Foden") of CRT, which had sponsored the phase I trial of temozolomide, about CRT's securing ownership of the rights to tetrazine derivatives. (D.I. 188 at 202:9-18) M&B and Cancer Research Campaign Technology ("CRCT"), a small subsidiary of CRT, executed a licensing agreement on March 26, 1991. (PTX-200)

28. CRCT could not commercialize temozolomide itself. After securing the patent rights, CRCT embarked on a "road show," a series of visits to pharmaceutical companies in the United States (including Schering), in an attempt to find a pharmaceutical partner to develop temozolomide. (D.I. 190 at 747:8-15) According to Foden, the phase I data for temozolomide was "critical" to attracting commercial success. (*Id.* at 776:3-20; PTX-612) "[T]o get a pharmaceutical company on board, [CRCT] needed a patent." (D.I. 190 at 752:4-5; 754:23-755:3)

29. Schering decided to pursue temozolomide. CRCT and Schering first entered into a "shutout agreement" to allow them to further negotiate the licensing of temozolomide. (PTX-202) Ultimately, the negotiations resulted in a June 1992 exclusive licensing agreement between the parties. (PTX-10 (U.S. rights); PTX-201 (non-U.S. rights)) Under that agreement, Schering pays CRCT a royalty percentage of net sales of temozolomide, and CRCT pays portions of that royalty to M&B, Aston University, and Charing Cross Hospital; the remainder is used to fund further cancer research. (D.I. 190 at 763:19-764:8)

30. After Schering and CRCT formalized their license agreement, responsibility for the '020 patent application was transferred to the law firm of Klauber & Jackson,

which handled other oncology applications for Schering.

31. On August 6, 1992, Examiner Richter issued an office action in the '020 application. With respect to 35 U.S.C. § 112, ¶ 1, Examiner Richter stated:

> The Board of Appeals and the CCPA have held that even though the specification does not mention human use specifically, the Patent Office is not precluded from finding an inference of human use and require proof thereof, when such use is of a medical nature [ ] for the treatment of serious disease, such as cancer. *Ex parte Moore et al.*, (POBA 1960) 128 U.S.P.Q. 8; *In re Citron*, (CCPA 1964) 325 F.2d 248, 139 U.S.P.Q. 516; *In re Hartop et al.*, (CCPA 1962) 311 F.2d 249, 135 U.S.P.Q. 541.
>
> Remission of a specific leukemia could be established, but has not been so accomplished or so claimed.

(PTX-2 at A174)

32. On February 5, 1993, Attorney Barbara L. Renda of Klauber & Jackson submitted, together with a request for an extension of time, a substantive response to the pending office action – the first filed in the entire chain of applications. With respect to the § 112, ¶ 1 rejection, Attorney Renda cited the relevant language of *Ex parte Krepelka* and asserted that

> [a] [c]omparison of the facts of *Krepelka* to those of the instant Application would lead to the inescapable conclusion that claims 1-28 are patentable to Applicants **based upon the results of animal testing given at lines 9-26 of page 8 and lines 1-8 at page 9**.

(PTX-2 at A193) (emphasis added) That is, despite the passage of over a decade, the applicants did not provide additional data in support of patentability; they pointed to animal data in the original specification.

33. On April 16, 1993, a Notice of Allowability was issued by Examiner Bernard Dentz, a Primary Patent Examiner. (PTX-2 at A198) Examiner Dentz provided the

following statement of reasons for allowance: "As evidence to support the utility of the instant compounds the article of Lunt and others from the Journal of Medicinal Chemistry is made of record." (*Id.*) This citation was to a 1987 article by inventor Lunt and others, entitled "Antitumor Imidazotetrazines. 14. Synthesis and Antitumor Activity of 6- and 8-Substituted Imidazo[5,1-d]-1,2,3,5-tetrazinones and 8-Substituted Pyrazolo[5,1-d]-1,2,3,5-tetrazinones"[19] (hereinafter, "the Lunt article"). (*Id.* at A201) The Lunt article was not cited by the applicants, but discovered independently by Examiner Dentz. It did not disclose human data, but showed activity of mitozolomide and other related compounds against tumors in mice.

34. The '291 patent issued on November 9, 1993. Schering submitted its investigational new drug application for temozolomide to the FDA on December 17, 1993. On August 11, 1999, the FDA granted Schering its first approval for Temodar® (temozolomide capsules); the indication was for the treatment of adult patients with refractory anaplastic astrocytoma ("AA"). (PTX-2 at A284) Between 2000 and 2004, Schering funded a study on the use of Temodar® for the treatment of glioblastoma multiforme ("GBM"); FDA approval for this use was granted in 2005. (D.I. 191 at 866:11-868:2) Barr did not file its ANDA (with Paragraph IV certification) until 2007.

B. Laches

1. The defense of prosecution laches

35. The first issue before the court is whether laches operates to render the '291 unenforceable. The Federal Circuit recognizes prosecution laches as a defense to

[19]J. Med. Chem., Vol. 30, pp. 357-66 (1987).

enforceability of a patent when it has issued after an "unreasonable and unexplained delay in prosecution." *See Symbol Techs., Inc. v. Lemelson Medical*, 277 F.3d 1361, 1363 & 1368 (Fed. Cir. 2002).

36. In *Symbol Technologies, Inc. v. Lemelson Medical, Education & Research Foundation*, 422 F.3d 1378 (Fed. Cir. 2005) (hereinafter, "*Symbol Techs.*"), the Federal Circuit explained that

> there are no strict time limitations for determining whether continued refiling of patent applications is a legitimate utilization of statutory provisions or an abuse of those provisions. The matter is to be decided as a matter of equity, subject to the discretion of a district court before which the issue is raised.

Id. at 1385.[20] A court must consider "the totality of the circumstances, including the prosecution history of all of a series of related patents and overall delay in issuing claims" in determining whether laches is triggered. *Id.* at 1386.

37. "There are legitimate grounds for refiling a patent application which should not normally be grounds for a holding of laches," such as filing "divisional applications on various aspects that the PTO has considered to be separate and distinct from each other," even when such filings are deferred until just before the issuance of the parent application. *Id.* at 1385. Other examples of legitimate practices given by the Federal Circuit are: refiling an application containing rejected claims (1) "in order to present evidence of unexpected advantages of an invention when that evidence may not have existed at the time of an original rejection"; or (2) to "add subject matter in order to

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[20]The defense was first recognized in 2002; the Federal Circuit did not expand upon its requirements until its 2005 decision.

attempt to support broader claims as the development of an invention progresses."[21] *Id.* In contrast, "refiling an application solely containing previously-allowed claims for the business purpose of delaying their issuance can be considered an abuse of the patent system." *Id.* (citation omitted). The "textbook case [of prosecution laches], if one exists, involves a patent application filed and then followed by a lengthy delay of unexplained **inactivity**." *Reiffin v. Microsoft Corp.*, 270 F. Supp. 2d 1132, 1156 (N.D. Cal. 2003) (citation omitted) (emphasis in original). The doctrine of prosecution laches "should be used sparingly lest statutory provisions be unjustifiably vitiated"; that is, "the doctrine should be applied only in egregious cases of misuse of the statutory patent system." *Symbol Techs.*, 422 F.3d at 1385.

2. The parties' arguments

38. Barr argues that CRCT unreasonably delayed prosecution by its conduct in filing eleven applications, effectuating ten abandonments, and frequently requesting extensions of time to respond to the PTO, resulting in nine years of total delay. CRCT asserts that the patent examiners required human clinical data and, absent such data, would not issue a patent. It was, according to CRCT, during the course of the prosecution of the chain of applications leading to the '291 patent that the standard evolved to permit animal testing to evidence patentability in this field of art. Further, Barr has not shown intervening rights, that is, it made no innovations relating to temozolomide during the prosecution of the applications at issue. Barr counters that there was no human data requirement, that the applicants never believed there was a

[21]The latter situation would necessitate the filing of continuation in part applications, rather than continuation applications.

human data requirement, and that the application was ultimately allowed based on animal data disclosed in the original specification. Only when CRCT had an opportunity to capitalize on the applications through its license with Schering did the applicants elect to challenge (and overcome) the utility rejection based on the original disclosures and longstanding precedent.

3. Discussion

a. Persuasive authority

39. In view of the very high standard propounded by the Federal Circuit, there are very few cases where prosecution laches has been asserted and discussed and even fewer where it has been found. The court finds the case at bar similar in some respects to *In re Bogese*, 303 F.3d 1362 (Fed. Cir. 2002), in which the Federal Circuit upheld a forfeiture decision by the Board. The application in that case claimed priority back to 1978. After two Board decisions and two rounds of appellate review, the applicant filed a series of eleven "file wrapper continuation applications" between 1987 and 1994. During this time, the applicant did not traverse the outstanding obviousness rejection. *Id.* at 1365.

40. The examiner issued a final rejection in the last application in which he expressly warned the applicant that the doctrine of laches would be invoked by "the next continuation of this series" of applications. The applicant did not heed this warning; he filed a twelfth continuation application in 1995, and the laches rejection was lodged. Thereafter, the applicant made his first substantive response to the examiner, in which he traversed the forfeiture rejection. The application was again rejected, and

the Board sustained the rejection. *Id.* at 1365-66. The Board found "the conduct of the appellant from March 1987 until September 18, 1995, which effectively permitted the applicant to retain the benefit of the filing date of June 14, 1978 while at the same time delaying prosecution of the application, [to be] so egregious in defeating the policy of the patent laws . . . as to be presumed unreasonable in light of all of the circumstances of this case." *Id.* Further, the Board noted that the applicant was "keenly aware, as early as the summer-fall of 1979, that [articles] embodying the appellant's invention were being developed and exploited commercially in the market place." *Id.* Upon review, the Federal Circuit affirmed the Board, stating that "the PTO has authority to forfeiture of rights for unreasonable delay" and that the Board's decision was not arbitrary "given that Bogese filed twelve continuation applications over an eight-year period and did not substantively advance prosecution of his application when required and given an opportunity to do so by the PTO." *Id.* at 1369.

41. In this case, CRCT also did nothing "to further the prosecution of [its] application toward the issuance of any claims" for nearly a decade and, instead, preserved its rights through a series of continuations and abandonments. *Id. In re Bogese* is distinguishable, however, in the respect that the PTO identified the laches and issued the forfeiture rejection administratively. The PTO did not similarly exercise its authority to reject CRCT's claims.

b. Intervening rights

42. CRCT emphasizes the fact that, unlike *In re Bogese*, there is no indication that Barr (or others) had "intervening rights." CRCT argues that Barr is precluded from

asserting prosecution laches by the fact that it did not itself invest in temozolomide in the 1982-1993 timeframe during which the chain of applications was pending. The court disagrees that the absence of "intervening rights" precludes Barr's prosecution laches defense. CRCT relies on *Symbol Technologies* for this proposition. (D.I. 198 at 35) In *Symbol Technologies*, the Federal Circuit noted that the district court in that case applied the doctrine of prosecution laches because Symbol had presented "strong evidence . . . of intervening private and public rights." 422 F.3d at 1382. The district court found that an 18- to 39-year time period had elapsed between the filing and issuance of the patents in suit, causing an "adverse effect on businesses that were unable to determine what was patented from what was not patented." *Id.* at 1386. "Accordingly," the Federal Circuit stated, "in this exceptional case, prejudice to the public as a whole has been shown here in the long period of time during which parties, including the plaintiffs, have invested in the technology described in the delayed patents." *Id.* The Federal Circuit concluded that the district court did not abuse its discretion in finding prosecution laches. *Id.*

43. Nowhere in its discussion did the Federal Circuit affirmatively impose a particular requirement that a competitor have invested in the technology claimed in order for prosecution laches to apply. Such a holding would be inconsistent with the Federal Circuit's general reluctance to impose "firm guidelines" (such as time limits) for determining when the equitable doctrine should apply. *Id.* at 1385. The *Symbol Technologies* Court's reluctance to overturn the district court's equitable decision does not represent a particular mandate, but general support for that court's concern for

eliminating "prejudice to the public as a whole." *Id.* at 1386.

44. On the other hand, *Symbol Technologies* supports the proposition that the lack of prejudice to Barr's commercial interests may be considered under the totality of the circumstances.

c. Discussion

45. Having determined that Barr's defense is not foreclosed by an "intervening rights" requirement, the issue at bar is whether, under the totality of the circumstances, CRCT's delay in prosecution was "unreasonable and unexplained," such as would constitute an "egregious case[ ] of misuse of the statutory patent system." *Id.* at 1385. Put another way, the court examines the reasonableness of CRCT's inaction vis-a-vis the Examiners' utility rejections.

46. There exists some level of ambiguity with respect to the office actions issued by Examiners Ford and Richter. The court cannot, in hindsight, determine what Examiners Ford and Richter believed regarding the statutory utility requirement between 1982 and 1993. It is true that neither Examiner expressly stated that human data was required. To some extent, this conclusion is inferrible by the Examiners' statements that the PTO "is not precluded from finding an inference of human use and require proof thereof" for claims directed to cancer treatments. In his first rejection (of the '656 patent), Examiner Ford also cited the 1957 District of Columbia decision of *Issenstead v. Watson*, 157 F. Supp. 7 (D.D.C. 1957), which expressed the opinion that "it is right and proper that the Patent Office should be very careful and perhaps even reluctant to grant a patent on a new medical formula until it has been thoroughly tested

and successfully tried by more than one physician[,]" because a patent "gives a kind of official imprimatur to the medicine in question on which as a moral matter some members of the public are likely to rely."

47. It would be equally reasonable to believe that in vitro or animal data may have satisfied that Examiner ("[n]o in vivo or in vitro tests" and "[n]o tests in laboratory animals" noted of record in rejecting the later '473 application). For obvious reasons, one cannot predict what would have resulted had the applicants responded substantively to any office action. Ultimately, it was Exarniner Dentz who found the Lunt article and who, in response to Attorney Renda's citation to animal data in the specification, allowed the claims in the '020 application.[22]

48. CRCT continuously emphasized at trial the importance of its temozolomide research. For such an important invention, there is not a shred of contemporaneous documentation – for example, memoranda, letters, notes or emails – evidencing that CRCT believed that its applications could not issue absent human data. Notwithstanding, CRCT's subjective belief is not relevant under *Symbol Technologies*, which contemplates only the objective reasonableness of the circumstances at bar.

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[22]The PTO had the initial burden of challenging utility. *See In re Marzocchi*, 439 F.2d 220, 223-24 (C.C.P.A. 1971). Only upon providing evidence casting doubt on the asserted utility would the burden have shifted to the applicants to present rebuttal evidence. *See In re Novak*, 306 F.2d 924, 928 (C.C.P.A. 1962). It appears that neither Examiners Ford nor Richter met his initial burden to cite evidence of non-utility in the first instance. Notwithstanding, Examiner Dentz's citation to the Lunt article (in **support** of patentability) was provided to buttress his conclusion that a person of ordinary skill in the art would not reasonably doubt the utility of the claimed invention based upon the disclosure of the specification. (PTX-2 at A198) ("As evidence to support the utility of the instant compounds the article of Lunt and others from the Journal of Medicinal Chemistry is made of record.")

See Reiffin, 270 F. Supp. 2d at 1153 ("It is an objective measure of reasonableness, applied to a patent applicant's explanation for his delay, that determines whether that delay is legitimate.").

49. Assuming that the Examiners required human data, and further giving CRCT the benefit of the doubt that it understood the rejections as requiring human data,[23] there are two problems with CRCT's position. First, CRCT never elected to challenge either Examiner's rejection (and, consequently, either validate its belief or obtain allowance of its claims) until it benefited CRCT commercially to do so. CRCT could have traversed the rejections on multiple occasions based on existing caselaw, but elected not to. The authority ultimately cited by Ms. Renda in support of patentability, *Ex Parte Krepelka*, 231 U.S.P.Q. 746 (B.P.A.I. 1986), was an August 1986 Board decision. The Board itself in that decision relied upon the 1969 decision of *In re Buting*, 418 F.2d 540 (C.C.P.A. 1969),[24] to support the statement that "[s]ubstantiating evidence [for utility purposes] may be in the form of animal tests which constitute recognized screening procedures with clear relevance to utility in humans." *Id.* Even older authority directly supported the patentability of CRCT's claims on the animal data presented. *In re Krimmel*, 292 F.2d 948, 953 (C.C.P.A. 1961) ("[W]e hold that when an applicant for a patent has alleged in his patent application that a new and unobvious

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[23]CRCT's witnesses so testified at trial. (D.I. 189 at 465:3-7; 587:19; 589:12-14; D.I. 190 at 754:8-10)

[24]"While the court's consideration of tests demonstrating effectiveness of compounds in treating diseases in animals indicates that such are not to be disregarded, it is clear that such tests must be viewed with respect to the utility asserted." *In re Buting*, 418 F.2d at 543.

chemical compound exhibits some potential useful pharmaceutical property and when this property has been established by statistically significant tests with 'standard experimental animals,' sufficient statutory utility for the compounds has been presented.").

50. Even if the argument that ultimately persuaded Examiner Dentz would not have persuaded either Examiners Ford or Richter, a subsequent rejection would have clarified either Examiner's position vis a vis human trials.[25] CRCT could have filed continuation applications following another rejection, even if made final. Ultimately, CRCT would have been in no worse position; its inaction is not justified in this respect.[26]

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[25]Sufficient confusion among PTO examiners on the issue is evidenced by the fact that the MPEP was amended in 1995 to iterate that "[o]ffice personnel should not impose on applicants the unnecessary burden of providing evidence from human clinical trials" to establish utility for the treatment of human disease. *See* MPEP § 2107.02(d), 6th Ed., Jan. 1995, Rev. 1, Sept. 1995 (available at http://www.uspto.gov/web/offices/pac/mpep/old/E6R1_2100.pdf). This language contrasts with the former MPEP § 608(p), cited *supra*, which provided that animal tests would be sufficient to overcome a utility rejection only where they were commonly accepted or accompanied by other evidence. In addition to striking down the notion of a human data requirement, the 1995 MPEP required only a "satisfactory" or "reasonable" correlation between the activity in question and the asserted utility to be demonstrated; "The fact that there is no known cure for a disease . . . cannot serve as the basis for a conclusion that such an invention lacks utility." *See* MPEP §§ 2107.02(c), (f).

[26]If CRCT believed that the utility rejection was valid, it could have pursued a partner to run human trials and obtain the data that the PTO required. There is no evidence that CRCT attempted to develop any of the claimed compounds prior to the "road show." Most likely, this was due to the fact that, as time went on, the toxicity of mitozolomide became more apparent. By 1991, M&B decided not to pursue studies with mitozolomide due to the toxic side effects seen in the Phase I trials. (D.I. 191 at 768:3-17) Phase I trials of mitozolomide began in 1983; results were first published in 1984. (PTX-79) The toxicity of mitozolomide was reported at least as early as 1987. (PTX-531) (reporting that two patients died due to toxicity and that no tumor remissions were achieved, and concluding that "mitozolomide produces unacceptable haematological toxicity and has no anti-tumor activity in previously treated patients with

51. It is the court's conclusion that the "ends" – commercialization of a very successful cancer drug – do not justify the "means" employed by CRCT in this case. Taken in the totality, this case involves eleven patent applications, ten abandonments, and no substantive prosecution for a decade. CRCT's primary justification for delay, that neither Examiner Ford nor Examiner Richter would have allowed the applications at issue absent human data, is not objectively reasonable in view of the fact that CRCT never attempted to traverse the rejections (thereby either validating its position or obtaining allowance of its claims). CRCT's delay, therefore, cannot "be explained by reference to [ ] legitimate considerations and/or expectations." *See Reiffin*, 270 F. Supp. 2d at 1155. CRCT introduced no contemporaneous evidence substantiating its position or establishing that CRCT sought to develop the technology prior to the Schering license. CRCT only engaged the PTO once it had a profit motive to do so. *Compare Symbol Techs.*, 422 F.3d at 1385 ("refiling an application solely containing previously-allowed claims for the business purpose of delaying their issuance can be considered an abuse of the patent system"). The court finds the conduct at bar sufficiently egregious to warrant rendering the '291 unenforceable due to prosecution laches. *Symbol Techs.*, 422 F.3d at 1385; *In re Bogese*, 303 F.3d at 1369.

C. Inequitable Conduct

1. Standards

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ovarian cancer.") CRCT's failure to inform the PTO of, inter alia, the toxicity of mitozolomide, a claimed compound, is discussed *infra* in the context of inequitable conduct.

52. Applicants for patents and their legal representatives have a duty of candor, good faith, and honesty in their dealings with the PTO. *Molins PLC v. Textron, Inc.*, 48 F.3d 1172, 1178 (Fed. Cir. 1995); 37 C.F.R. § 1.56(a). This duty is predicated on the fact that "a patent is an exception to the general rule against monopolies and to the right of access to a free and open market." *Precision Instrument Mfg. Co. v. Auto. Maint. Mach. Co.*, 324 U.S. 806, 816 (1945). The duty of candor, good faith, and honesty includes the duty to submit truthful information and the duty to disclose to the PTO information known to patent applicants or their attorneys which is material to the examination of a patent application. *Elk Corp. of Dallas v. GAF Bldg. Materials Corp.*, 168 F.3d 28, 30 (Fed. Cir. 1999). A breach of this duty constitutes inequitable conduct. *Molins*, 48 F.3d at 1178.

53. If it is established that a patent applicant engaged in inequitable conduct with respect to one claim, then the entire patent application is rendered unenforceable. *Kingsdown Med. Consultants v. Hollister Inc.*, 863 F.2d 867, 877 (Fed. Cir. 1988). Additionally, "[a] breach of the duty of candor early in the prosecution may render unenforceable all claims which eventually issue from the same or a related application." *Fox Indus., Inc. v. Structural Pres. Sys., Inc.*, 922 F.2d 801, 803-04 (Fed. Cir. 1990).

54. A finding of inequitable conduct is "an equitable determination" and, therefore, "is committed to the discretion of the trial court." *Monon Corp. v. Stoughton Trailers, Inc.*, 239 F.3d 1253, 1261 (Fed. Cir. 2001). In order to establish unenforceability based on inequitable conduct, a defendant must establish by clear and convincing evidence that: (1) the omitted or false information was material to

patentability of the invention; (2) the applicant had knowledge of the existence and materiality of the information; and (3) the applicant intended to deceive the PTO. *Molins*, 48 F.3d at 1178. A determination of inequitable conduct follows a two-step analysis. The withholding of information must first meet threshold findings of materiality and intent. *Id.*

55. The Federal Circuit has recently stated that, prior to 1992, two standards for materiality were in effect: (1) the materiality standard set forth in the present version of PTO Rule 56, 37 C.F.R. § 1.56(b); and (2) the previous version of that rule. *See Digital Control Inc. v. Charles Machine Works*, 437 F.3d 1309, 1314 (Fed. Cir. 2006). The Court in *Digital Control* held that the new 1992 iteration of Rule 56 was not intended to replace the broader old Rule 56, and "merely provides an additional test of materiality." *Id.* at 1316. Therefore, "if a misstatement or omission is material under the new Rule 56 standard, it is material. Similarly, if a misstatement or omission is material under the 'reasonable examiner' standard or under the older three tests, it is also material." *Impax Labs., Inc. v. Aventis Pharm. Inc.*, 468 F.3d 1366, 1374 (Fed. Cir. 2006) (quoting *Digital Control*, 437 F.3d at 1316)).

56. Rule 56 formerly provided that "information is material where there is a substantial likelihood that a reasonable examiner would consider it important in deciding whether to allow the application to issue as a patent." 37 C.F.R. § 1.56 (1990). The inquiry presented under the prior "reasonable examiner" standard is whether "a reasonable examiner would have considered such [omitted] prior art important in deciding whether to allow the patent application." *Impax Labs.*, 468 F.3d at 1374

(quoting *Digital Control*, 437 F.3d at 1314)).

57. The applicable "older three tests" referenced in *Digital Control* include: (1) the objective "but-for" standard, in other words, "where the misrepresentation was so material that the patent should not have issued;" (2) the subjective "but-for" test, in other words, "where the misrepresentation actually caused the examiner to approve the patent application when he would not otherwise have done so;" and (3) the "but it may have" standard, "where the misrepresentation may have influenced the patent examiner in the course of prosecution." *See Impax Labs.*, 468 F.3d at 1374, n.5 (quoting *Digital Control,* 437 F.3d at 1315)).

58. Currently, Rule 56 is narrower in scope:

> Information is material to patentability when it is not cumulative to information already of record or being made of record in the application, and
>
> (1) It establishes, by itself or in combination with other information, a prima facie case of unpatentability of a claim; or
>
> (2) It refutes, or is inconsistent with, a position the applicant takes in:
> (i) Opposing an argument of unpatentability relied on by the Office, or
> (ii) Asserting an argument of patentability.

37 C.F.R. § 1.56(b) (2007).[27]

59. After determining that the applicant withheld material information, the court

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[27]Further,

> [a] prima facie case of unpatentability is established when the information compels a conclusion that a claim is unpatentable under the preponderance of evidence, burden-of-proof standard, giving each term in the claim its broadest reasonable construction consistent with the specification, and before any consideration is given to evidence which may be submitted in an attempt to establish a contrary conclusion of patentability.

37 C.F.R. § 1.56(b) (2007).

must decide whether the applicant acted with the requisite level of intent to mislead the PTO. *See Baxter Int'l, Inc. v. McGaw Inc.*, 149 F.3d 1321, 1327 (Fed. Cir. 1998). "Intent to deceive cannot be inferred solely from the fact that information was not disclosed; there must be a factual basis for finding a deceptive intent." *Hebert v. Lisle Corp.*, 99 F.3d 1109, 1116 (Fed. Cir. 1996). That is, "the involved conduct, viewed in light of all the evidence, including evidence indicative of good faith, must indicate sufficient culpability to require a finding of intent to deceive." *Kingsdown*, 863 F.2d at 876. A "smoking gun" is not required in order to establish an intent to deceive. *See Merck*, 873 F.2d at 1422. An inference of intent, nevertheless, is warranted where a patent applicant knew or should have known that the withheld information would be material to the PTO's consideration of the patent application. *Critikon, Inc. v. Becton Dickinson Vascular Access, Inc.*, 120 F.3d 1253, 1256 (Fed. Cir. 1997).

60. Once materiality and intent to deceive have been established, the trial court must weigh them to determine whether the balance tips in favor of a conclusion of inequitable conduct. *N.V. Akzo v. E.I. DuPont de Nemours*, 810 F.2d 1148, 1153 (Fed. Cir. 1987). The showing of intent can be proportionally less when balanced against high materiality. *Id.* In contrast, the showing of intent must be proportionally greater when balanced against low materiality. *Id.*

61. Because a patent is presumed valid under 35 U.S.C. § 282, inequitable conduct requires proof by clear and convincing evidence. *Manville Sales Corp. v. Paramount Sys., Inc.*, 917 F.2d 544, 551 (Fed. Cir. 1990).

2. Materiality

62. Barr asserts that inventor Stevens and attorneys Bentham, Miller, Mosher, and Renda committed inequitable conduct by failing to disclose both phase I and phase II mitozolomide date establishing that, for certain cancers, mitozolomide was not beneficial.

63. The '291 patent contains broad claims to treating various cancers. For example:

> 28. A method for the treatment of a patient with a malignant neoplasm such as **a carcinoma**, melanoma, sarcoma, lymphoma or leukemia which comprises administering to the patient a tetrazine derivative as claimed in claim 1 in an amount sufficient to improve for the better the condition of the patient.

(emphasis added) Other method claims are broadly directed to treating immunological disease (claim 29), malignant neoplasm (claim 30), leukemia (claim 31), glioma (claim 32), and mycosis fungoides (claim 33). The specification discloses that the compounds of formula 1 (claimed in claim 1) "possess **valuable** antineoplastic activity, for example against carcinomas, melanomas, sarcomas, lymphomas and leukemias." ('291 patent, col. 4:29-32) (emphasis added) The patent states that the compounds "possess **useful** activity against glioma and mycosis fungoides." (*Id.*, col. 4:32-33, col. 12:48-53) (emphasis added) They are "**particularly active** in mice . . . against TLX5 (S) lymphomas," and are "active" against "leukemia L1210." (*Id.*, col. 4:33-46) (emphasis added) The compounds are also "active" against "B16 melanoma and C38 tumor in mice." (*Id.*, col. 4:49-50)

64. The specification notes that the compounds tested against TLX5 tumors were administered according to a procedure described by Gescher et al., and "ADJ/PC6A and M5076" tests. (*Id.*, col. 4:36-39) The compounds were "grafted

intraperitoneally, intracerebrally and intravenously" in the studies with leukemia L1210, B16 melanoma and C38 tumor according to the "NCI Monograph 45" procedure. (*Id.*, col. 4:42-43, 4:50) The NCI Monograph 45 protocol discloses measuring activity as an expression of T/C%. (PTX-63; D.I. 190 at 705:11-16) A T/C% value greater than or equal to 125 is necessary to demonstrate activity according to this protocol. (D.I. 190 at 706:2-7) The '291 patent specification does not expressly correlate activity against any of the named cancers to a T/C percent value.

65. The '291 patent specification identifies compounds A-M as "**[i]mportant** individual compounds" of general formula I, and states that "[c]ompounds A and D, and especially C, are of **particular importance**." ('291 patent, col. 4:57-58, col. 5:17-18) (emphasis added) Compound A is temozolomide (the active ingredient in Temodar®); compound C is mitozolomide (the first compound tested by the applicants in animals and humans); and compound D is a mitozolomide-related compound (a mitozolomide with a methyl group on the carbonyl ring). (D.I. 188 at 178:15; D.I. 189 at 445:13-21) Each compound is individually claimed.

66. Despite the inactivity on the part of the applicants, the prosecution of applications leading to the '291 patent was open and ongoing from 1982 to the '291 patent's issuance in 1993. The duty of disclosure was present during this entire timeframe.[28]

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[28]The court notes (and dismisses) at this juncture CRCT's argument that data and articles post-dating the filing date of the '656 application are not relevant to inequitable conduct insofar as enablement and utility are determined at the time of filing. It is black letter law that the duty of candor applies throughout a patent's prosecution. *See, e.g., Fox Indus., Inc. v. Structural Preservation Sys., Inc.*, 922 F.2d 801, 803 (Fed. Cir. 1991); MPEP § 2001.06; 37 C.F.R. § 1.56. The withheld

67. Data evidencing the inactivity of several of the compounds A-M was in the possession of Aston University, where Stevens and Stone were conducting research, as early as 1982. (PTX-70 at 1536 (T/C% < 125, compound B); *id.* at 1537 (T/C% < 125, compound K))[29]

68. A handwritten chart comparing the activities of several mitozolomide analogs, dated July 19, 1983, was introduced at trial.[30] (DTX-184) Activity data was noted against TLX5 tumors. Structures corresponding to compounds B, E, F, G, J, and K, having T/C% values under 125, were labeled "inactive." (*Id.*; DX-DEMO102) The notes indicate that many of these structures were "sent to" "Aston." (*Id.*)

69. In 1985, Stevens and Stone co-authored a publication specifically stating that mitozolomide, temozolomide, and a 3-(2-bromethyl-)derivative had "marginal" activity against TLX5 lymphoma in mice; the "other 3-alkyl analogues [tested] are **all inactive** against this tumor on a single dose schedule." (DTX-576 at 437)[31] (emphasis added) Among the reportedly inactive compounds (having a T/C% < 125) were

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information at issue was "a verification of the patented technology," as compared to "basic scientific research" that did not attempt to test the patented invention. *Compare Research Corp. Technologies, Inc. v. Microsoft Corp.*, 536 F.3d 1247, 1252 (Fed. Cir. 2008) (holding the latter type of experiment not material where the research was not necessary to practice the patented invention).

[29]This same document evidences activity for compound D. (PTX-70 at 1475 (T/C% > 254 and T/C% > 555))

[30]Stevens testified that the notes came from his files; he believed the chart originated from M&B. He was able to identify several of the M&B compound codes appearing in the chart. (D.I. 189 at 257-61)

[31]S.P. Langdon et al., *Structure-activity relationships in antitumor 3-alkylimidazo-tetrazinones*, The British Journal of Cancer, vol. 52, no. 3 at 437 (Sept. 1985) (abstract introduced as DTX-576).

compounds B, E, F, G, J and K.[32] (*Id.*; DX-DEMO106)

70. While activity for mitozolomide against adenocarcinoma of the ovary (phase I study) and malignant melanoma (phase II study) had been reported prior to 1986 (PTX-79 at 704; PTX-80), Stevens authored several publications between 1986 and 1987 indicating contrary results in other cancers.

71. In 1986, Stevens and his colleagues submitted an article to the Cancer Research Journal in which the activity of several experimental compounds on the TLX5 tumor strain in mice was noted. (PTX-77, table 2) Structures corresponding to claimed compounds B, K, E, F, and G were reported to have a T/C% value under 125. (*Id.*; DX-DEMO101 at A1475)

72. A 1987 book chapter authored by Stevens[33] included a table specifically listing six of the "important" mitozolomide analogs of the '291 patent as "inactive." (PTX-83) A 1990 book chapter co-authored by Stevens, Newlands and Blackledge[34] describes the phase II studies undertaken with mitozolomide as follows.

> A number of phase II studies were performed with mitozolomide in the following diseases: colorectal and breast carcinoma, bladder cancer, ovarian adenocarcinoma, and renal cell carcinoma, and all these phase II studies were **negative with no responses being seen** and varying degrees of

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[32]The same information is conveyed in an undated paper by Stevens, entitled "Second generation imidazotetrazinones." Plaintiffs represented that this paper originated from Stevens' files; Stevens testified that he recognized the drawings as his own. (DTX-492 at 1808; D.I. 188 at 239-40)

[33]Malcolm F. G. Stevens, *Second Generation Azolotetrazinones, in* NEW AVENUES IN DEVELOPMENTAL CANCER CHEMOTHERAPY, 335, 340-41 (Academic Press, Inc. 1987) (PTX-83).

[34]E.S. Newlands et al., *Experimental Background and Early Clinical Studies with Imidazotetrazine Derivatives, in* TETRAZINES, 185 (Plenam Press, 1990) (PTX-67).

myelosupression being dose-limiting.

> However, not all the phase II studies with mitozolomide showed no evidence of activity. Some activity was seen in malignant melanoma [citation to the article of record at PTX-80]. In addition, some activity was seen in small cell carcinoma of the lung. In a summary of the clinical data to May 1986, 221 patients had been treated with 146 available for assessment of response, giving a total of 2 complete responses and 6 partial responses (all these responses being seen in malignant melanoma and small cell carcinoma of the lung).

(PTX-67 at 187) (emphasis added)

73. Papers documenting these cited unsuccessful studies were admitted during trial. A 1987 article[35] discussed the treatment of 25 (previously treated) advanced ovarian cancer patients with mitozolomide. It was reported that two patients died due to toxicity and that no tumor remissions were achieved, and it was concluded that "mitozolomide produces unacceptable haematological toxicity and has no anti-tumor activity in previously treated patients with ovarian cancer." (PTX-531)

74. Similarly, a 1988 article[36] reported phase II results for twenty-two patients with advanced colorectal cancer and fourteen with breast cancer, noting no response, and concluding that "mitozolomide. . . does not show activity in human CRC [colorectal cancer] and in pretreated BC [breast cancer]," not precluding a "marginal activity of the drug as a first line therapy in [breast cancer]." (PTX-530) Another 1988 phase II study of fifteen patients with advanced bladder cancer resulted in no responses and

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[35]J.P. Neigt et al., *Mitozolomide in Patients With Advanced Ovarian Carcinoma: A Phase II Study of the EORTC Gynecological Cancer Cooperative Group*, Proceedings ECCO (April 1987) (PTX-531).

[36]P. Heriat et al., *Phase II study of mitozolomide (M & B 39,565) in colorectal and breast cancer,* Investigational New Drugs 6:323-25 (1988) (PTX-530).

unacceptable myelotoxicity.[37] (PTX-66) It was noted that "[r]esponses to mitozolomide have been seen in lung cancer and melanoma but other tumor types appear to be resistant to the doses that can be reasonably administered." (*Id.*) A 1989 phase II study for mitozolomide in treating patients with advanced renal cell carcinoma yielded no complete or partial responses.[38] (PTX-81)

75. The applicants never disclosed to the PTO any data or publications indicating that the "particular[ly] importan[t]" compound mitozolomide, as disclosed in the '291 specification, did not treat colorectal and breast carcinoma, bladder cancer, ovarian adenocarcinoma, or renal cell carcinoma, encompassed by the broad "carcenoma, melanoma, sarcoma, lymphoma or leukemia" classes named in claim 28. The PTO was also never informed that several of the purportedly "important" mitozolomide analogs, such as compounds B, E, F, G, J, and K, were considered (by the inventors themselves)[39] to be "inactive" in at least TLX5 lymphoma,[40] as

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[37]G. Blackledge et al., *A Phase II Study of Mitozolomide in Metastatic Transitional Cell Carcinoma of the Bladder*, Eur. J. Cancer Clin. Oncol., Vol. 25, No. 2, pp. 391-92 (1989) (accepted for publication September 29, 1988) (PTX-66).

[38]A. Van Oosterom et al., *Mitozolomide in Advanced Renal Cancer, A Phase II Study in Previously Untreated Patients from the EORTC Genito-Urinary Tract Cancer Cooperative Group*, Eur. J. Cancer Clin. Oncol., Vol. 25, No. 8, pp. 1249-50 (1989) (accepted for publication April 12, 1989) (PTX-81).

[39]Stevens, Newlands and Blackledge's 1990 book chapter evidences that at least these three inventors were aware of these negative results, if not the precise publications containing them.

[40]That this data was animal (mouse) data is not distinguishing. CRCT ultimately obtained patentability based on the mouse data disclosed in the specification. CRCT cannot credibly argue that, for purposes of inequitable conduct, animal data is not the type of information an examiner would have liked to have had before him. In other words, the references are no less material based on the fact that they concern results in

encompassed by claim 28. Prior to the '291 patent's issuance in 1993, the applicants never disclosed to the PTO that mitozolomide had a demonstrable toxicity in phase II trials.

76. The court notes CRCT's arguments that the phase I data was not material because those trials focus on "safety, not efficacy;" and the phase II data was "preliminary and/or inconclusive." (D.I. 198 at 45-46) These arguments are belied by the fact that Stevens: (1) thought the data was significant enough to describe in publications to the scientific community; (2) did not characterize the data as "preliminary" or similar; and (3) did not qualify, in any manner, his conclusion regarding "inactiv[ity]" (or "no evidence of activity").

77. It is the court's conclusion, therefore, that the withheld information directly contradicts statements made in the '291 patent's specification regarding the utility of the claimed compounds, and directly contravenes the patentability of (broadly-written) claim 28. For these reasons, the withheld inactivity data is highly material.[41]

78. Finally, the court notes that CRCT's assertions that certain (nondisclosed) positive studies are "cumulative to the disclosure in the specification" and support utility

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mice.

[41]The court notes that, when the '020 application was finally prosecuted, the applicants argued that "oncologists treating malignant neoplasms, given applicants' teaching, would easily select an appropriate compound, make said compound, formulate it for appropriate administration, and then administer it according to the treatment required by the particular neoplasm in accordance with the taught dosage range." (PTX-2 at A195) It is the court's understanding that carcinomas are a subset of cancers encompassed by the term "neoplasms." Assuming this is the case, the withheld information also directly contradicts this statement to the extent it does not limit the "appropriate compound" to any particular compound (A-M) and implies that each compound works to treat neoplasms.

of certain of the claims (D.I. 198 at 47-48) is misplaced. Materiality is not adjudged by whether the withheld information is "positive" or "negative;" to the extent CRCT had positive phase II data (regarding malignant melanoma and/or small cell carcinoma of the lung), it was also information that "may have influenced the patent examiner in the course of prosecution."[42] *See Impax Labs.*, 468 F.3d at 1374, n.5 (quoting *Digital Control*, 437 F.3d at 1315)). The withheld positive results are also material, although not highly material. The positive data does not mitigate against either the fact that the data was withheld, or against the materiality of the withheld negative data.

3. Intent

79. "An inference of intent to deceive is generally appropriate . . . when (1) highly material information is withheld; (2) the applicant knew of the information [and] . . . knew or should have known of the materiality of the information; and (3) the applicant has not provided a credible explanation for the withholding." *Praxair, Inc. v. ATMI, Inc.* 543 F.3d 1306, 1314 (Fed. Cir. 2008) (internal quotations and citations omitted).

80. The court has determined that the information withheld from the PTO was highly material, and that (at least) Stevens knew of the information. Stevens should have appreciated the materiality of the data and his conclusions as they expressly contradicted the disclosure of the pending applications.

81. CRCT's explanations for Stevens's withholding are as follows: (1) Stevens

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[42]Under the 1990 standard, there was "a substantial likelihood that a reasonable examiner would consider it important in deciding whether to allow the application to issue as a patent." 37 C.F.R. § 1.56 (1990). Under either standard, the positive results may have influenced Examiners Ford or Richter to allow certain of the claims, even if in amended form.

published more than 40 papers on tetrazine derivatives; (2) Stevens considered phase I and phase II data "confidential to clinicians" (D.I. 188 at 213:11-13); (3) the mitozolomide phase II studies were not conclusive; and (4) "there was no relevant prior art to disclose." (D.I. 198 at 52-54) These explanations are belied by the facts that Stevens found the data conclusive enough (and sufficiently non-confidential) to publish the data and his conclusions of inactivity or toxicity to the scientific community. Stevens did not qualify his statements regarding inactivity. Certainly, if Stevens found the information sufficiently accurate to base conclusions upon and to publish to his peers, it was sufficiently accurate and conclusive enough to submit to the PTO.

82. CRCT cites case law that "[p]ublication is an act inconsistent with an intent to conceal data from the PTO." *Research Corp.*, 536 F.3d at 1252. Although this may be the case in certain circumstances, there is also authority to the contrary. *See Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc.*, 326 F.3d 1226, 1241 (Fed. Cir. 2003) (applicants' "duty of disclosure was to the PTO and publishing the article did not amount to [ ] disclosing the article to the PTO"). Under these circumstances, the court finds Stevens' publications to the scientific community a sufficient basis upon which to infer an intent to deceive.[43] *See Ranbaxy Labs. Ltd. v. Abbott Labs.*, Civ. Nos. 04-8078 & 05-1490, 2005 WL 3050608, *9 (N.D. Ill. Nov. 10, 1995) (finding a substantial

[43]Stevens received a milestone payment for his work in 1992, and currently receives a portion of the royalties on Temodar® from Aston University. (D.I. 188 at 123:20-25) It is unclear whether this arrangement was part of the June 1992 license agreement with Schering, or when Aston University notified Stevens of this compensation. Thus, it cannot be said definitively that Stevens also had a financial motivation to withhold the material information from the PTO prior to the '291 patent's issuance.

likelihood of an intent to deceive and awarding preliminary injunction where inventors published material information and submitted it to the FDA, but not the PTO).

83. Miller testified that he would have explained to the inventors their duty of disclosure; Stone recalled a meeting with Miller where Miller explained the patent process. (D.I. 190 at 729:1-3; D.I. 191 at 962:17-18) Each inventor signed a declaration acknowledging the duty of candor. (PTX-3 at A474-75) At trial, Miller admitted that, evidently, "there was a breakdown in [his] system for dealing with the duty of disclosure"; he did not receive all of Stevens' publications. (D.I. 190 at 667:3-11) The court agrees that something was awry, insofar as not a single piece of data or prior art, positive or negative, was provided to the PTO in over eleven years (despite over a decade's worth of research on the technology). It is the court's finding that Stevens committed inequitable conduct by failing to disclose, in accordance with his duty, the information discussed *supra*. In view of this determination, the court need not address Barr's arguments with respect to Bentham, Mosher, Miller, or Renda.

III. CONCLUSION

84. For the reasons discussed above, the court finds the '291 patent unenforceable due to prosecution laches and/or inequitable conduct.