

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 Examiner 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.<sup>22</sup>

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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<sup>22</sup>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,<sup>23</sup> 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),<sup>24</sup> 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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<sup>23</sup>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)

<sup>24</sup>“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.<sup>25</sup> 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.<sup>26</sup>

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<sup>25</sup>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](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).

<sup>26</sup>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).<sup>27</sup>

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

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<sup>27</sup>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 data 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.<sup>28</sup>

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<sup>28</sup>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))<sup>29</sup>

68. A handwritten chart comparing the activities of several mitozolomide analogs, dated July 19, 1983, was introduced at trial.<sup>30</sup> (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)<sup>31</sup> (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).

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

<sup>30</sup>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)

<sup>31</sup>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.<sup>32</sup> (*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<sup>33</sup> 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<sup>34</sup> 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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<sup>32</sup>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)

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

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

myelosuppression 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<sup>35</sup> 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<sup>36</sup> 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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<sup>35</sup>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).

<sup>36</sup>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.<sup>37</sup> (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.<sup>38</sup> (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)<sup>39</sup> to be “inactive” in at least TLX5 lymphoma,<sup>40</sup> as

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<sup>37</sup>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).

<sup>38</sup>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).

<sup>39</sup>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.

<sup>40</sup>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.<sup>41</sup>

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.

<sup>41</sup>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.”<sup>42</sup> 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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<sup>42</sup>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.<sup>43</sup> 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

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<sup>43</sup>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.