09-1832-cv

In the
United States Court of Appeals
For the Second Circuit

HIFI DNA TECH LLC,

Plaintiff-Appellant,

– v. –

UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES, UNITED STATES FOOD & DRUG ADMINISTRATION, KATHLEEN SEBELIUS, O/, SEC. OF U.S. HEALTH AND SVCS., MARGARET HAMBURG, O/, COMM. OF U.S. FOOD & DRUG ADMIN.,

Defendants-Appellees.

ON APPEAL FROM THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF CONNECTICUT

BRIEF FOR PLAINTIFF-APPELLANT

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RULE 26.1 CORPORATE STATEMENT

Plaintiff Appellant HIFI DNA TECH, LLC, states that no corporation owns 10% or more of the stock or interest in Plaintiff.

TABLE OF CONTENTS

TABLE OF AUTHORITIES

JURISDICTIONAL STATEMENT

The district court had subject matter jurisdiction of this case under the Administrative Procedures Act, 5 U.S.C.A. § 701 et seq. as a final order from a federal agency. The Food and Drug Administration denied Plaintiff's petition for reclassification of Plaintiff's medical device. FDA's denial was the agency's final decision as to the petition, and no other administrative remedies were available.

This Court has jurisdiction under 28 U.S.C.A. § 1291 as an appeal from a final order of a district court that disposed of all parties' claims. The district court ruled in favor of Defendants' Motion to Dismiss on March 24, 2009 and a Notice of Appeal was timely filed on April 22, 2009.

STATEMENT OF THE ISSUES PRESENTED FOR REVIEW

1. Did the District Court properly grant the motion for judgment without taking any evidence in a case where Plaintiff showed many of the findings of Defendants lacked scientific basis?

2. Did the District Court properly find that Defendants did not act arbitrarily and capriciously and did not abuse their discretion?

STATEMENT OF THE CASE

Plaintiff filed a petition with FDA seeking to reclassify its medical device from Class III to Class II. FDA denied the petition. Plaintiff sued FDA (and related governmental parties) under the Administrative Procedures Act, asserting that FDA acted arbitrarily and capriciously in denying the petition. FDA responded by filing a motion to dismiss the complaint on the grounds that Plaintiff failed to state a claim. The district court granted the motion, dismissing Plaintiff's case. This appeal followed.

LOCAL RULE 28 PRELIMINARY STATEMENT:

The Honorable Alfred V. Covello rendered the decision appealed from, which can be found in the Joint Appendix at page 72. The opinion is not reported. His opinion upheld the agency decision rendered by Dr. Steven Gutman, Director of the Office of In Vitro Diagnostic Device Evaluation and Safety at the Food and Drug Administration, found in the Joint Appendix at page 55.

STATEMENT OF FACTS

Plaintiff manufactures a medical device for the detection of Human Papillomavirus, commonly known as HPV. JA 74.[1] The device uses DNA polymerase chain reaction technology (PCR), which means that the device copies the targeted DNA many times ("amplifies" the DNA) for the purpose of detection. AR 102. If the target DNA is present, it can also be genotyped, meaning that the specific type of DNA being amplified can be identified using further tests, such as DNA sequencing. AR 136. After detection, Plaintiff's device prepares materials for genotyping, but does not perform HPV genotyping. AR 102. There are more than 100 genotypes of HPV. AR 138.

Plaintiff filed a petition for reclassification of its device from Class III (requiring premarket approval before it could be marketed) to Class II on March 7, 2007. JA 31. Because FDA did not rule on the petition within the 210 day statutory time period, Plaintiff filed a mandamus action on October 12, 2007 to compel FDA to issue a ruling. *See* HIFI v. FDA, 3:07CV1511RNC, Dist. Court Conn. (no opinion issued). The mandamus action was moot when FDA issued a denial of the petition on December 14, 2007.

Class III devices are subject to FDA's strictest regulations. JA 74. Class III devices must obtain premarket approval from FDA, a process in which the

[1] "JA" refers to the Joint Appendix, and "AR" to the administrative record.

applicant must demonstrate a reasonable assurance that the device is safe and effective. JA 74. A new device can avoid this procedure if it can be reclassified as Class I or Class II. JA 74.

According to sources cited by the FDA, which sources Plaintiff does not dispute, HPV is a virus often found in the lower genital tract and usually spread by sexual contact. JA 22. The virus is common, and the lifetime likelihood of contracting the virus is estimated at 75-90%. JA 23. Although the vast majority of women who contract HPV have no symptoms and the infections will clear by themselves (JA 24), some types of HPV, known as high risk types, have been linked to cancer. JA 24. However, for such an infection to actually cause cancer, it must be a persistent infection with a high risk HPV type. JA 24. Even then, such an infection may, but does not necessarily, result in abnormal cell growth which may, but does not necessarily, result in cancerous cells. JA 24. It is only this persistent infection with high risk HPV types that is linked to cancer. JA 24. Consequently, for an HPV infection to have even the potential to cause cancer, it must (1) be one of the minority that does not clear on its own, (2) be a high risk type and (3) be persistent, as indicated by repeat testing positive for the same high risk genotype of HPV over a period of time. AR 103. Even then, it will take months (sometimes years) of such an infection before the virus can replicate

enough to possibly cause cancer. JA 22.

Plaintiff's device replicates all types of HPV DNA, not just the high risk types. AR 119. If the device detects any type of HPV, then it would prepare the materials for a secondary test, such as DNA sequencing that, would determine specifically which type of HPV was present. AR 112. DNA sequencing is not part of the plaintiff's device. AR 137. The plaintiff's device is to be used together with other genotyping tests, preferably the DNA sequencing technology and under a physician's supervision to ensure safety and effectiveness. AR 112. For comparison, the Digene HC2 device, which is the latest FDA approved stand-alone HPV testing device, detects the presence of 13 high risk HPV types as a group, but cannot identify any specific type of HPV. JA 29.

Plaintiff tested the device against the Digene HC2, and Plaintiff's device used together with DNA sequencing outperformed Digene's. AR 142-148. Out of 513 patient samples, the device detected 107 cases of HPV, including 74 high risk cases, while the Digene test detected only 67 cases, including 50 high risk cases. AR 144-148. Significantly, Plaintiff's device used together with DNA sequencing detected all of the high risk cases Digene's device detected (in other words, Plaintiff's device did not miss any Digene hits, but Digene missed many of Plaintiff's hits), showing that the device has fewer false negatives (if any) than the

latest device approved by FDA for HPV testing. AR 144. Although Digene's device is the most recently approved of all HPV testing devices, it still uses nucleic acid hybridization assay technology first approved in 1988. JA 28-29. Further, Plaintiff's device could detect as few as 10 copies of target DNA, while Digene's could only operate with approximately 100,000 copies of DNA present. AR 114. The results of these tests were reproduced in parallel testing to confirm accuracy. AR 149. Further, the all positive PCR results were confirmed by DNA sequencing, proving that the DNA identified was that of HPV, each validated by the GenBank sequence database for specific HPV genotyping. AR 140.

In spite of the above, FDA denied the petition, claiming that (1) the supporting data provided by Plaintiff was inadequate, (2) the special controls Plaintiff suggested for the use of the device did not provide reasonable assurances of safety and effectiveness, and (3) insufficient information existed to establish adequate special controls. JA 58. Although Plaintiff requested that it be given an opportunity to address any questions or concerns during the petition process, Plaintiff was given no opportunity to respond to these assertions or otherwise address FDA's concerns. JA 8, ¶12.

The district court affirmed the petition denial, stating that the findings of FDA contained in its 14 page denial were not arbitrary and capricious. JA 83. The district court did not allow Plaintiff to show, through the use of other scientific

sources not cited by FDA, that FDA's analysis was contrary to the current state of science and simply incorrect in many of its statements and conclusions.

SUMMARY OF THE ARGUMENT

The district court should have denied FDA's motion. Rather, the district court should have reviewed the pleadings and allowed some hearing and evidence outside the record to be taken. Most cases of agency review contain only issues of law because the facts were established at the agency level. But in this case facts outside the administrative record were necessary to review the agency's decision to explain and clarify the technical matter involved in the agency action and to evaluate the apparent improper behavior on the part of the agency decision makers. Because Plaintiff was simply issued a denial without any opportunity to dispute errors of fact or law at the agency level, the district court should have permitted some discovery and taken evidence to evaluate the appropriateness of FDA's decision.

FDA abused its discretion in issuing the denial. FDA made several errors of fact and conclusions based thereon in denying the petition. Specifically, FDA applied scientific principles to Plaintiff's device that are simply not applicable to the device. Further, FDA repeatedly asserts that the device is a cancer test, when it is simply a test to determine the presence of a common virus. The denial was an abuse of discretion and should be reversed.

ARGUMENT

I. THE DISTRICT COURT SHOULD NOT HAVE GRANTED FDA'S MOTION BUT RATHER SHOULD HAVE ALLOWED PLAINTIFF TO PRESENT EVIDENCE OUTSIDE OF THE ADMINISTRATIVE RECORD TO DISPUTE FDA'S CONCLUSIONS.

The district court erred in granting FDA's motion in light of the factual allegations in the pleadings that gave rise to issues outside of the administrative record. This Court reviews the district court's grant of the motion for judgment *de novo*. Patel v. Contemporary Classics of Beverly Hills, 259 F.3d 123, 126 (2nd Cir. 2001).

Plaintiff's complaint asserted many facts showing that FDA's denial of its petition was arbitrary and capricious, the product of misapplied science, and possibly the product of bad faith. For example, Plaintiff pled that it sent a letter requesting the opportunity to appear before any panel of scientists reviewing the petition, but never heard from FDA. JA 8, ¶12. Plaintiff requested a copy of a 1988 FDA order cited by FDA as reason for designating the device as Class III, but never heard from FDA. JA 15, ¶11. Plaintiff made numerous assertions in paragraph 15 of the Amended Complaint that would require review of information FDA failed to place in the record, including but not limited to:

> b. The denial improperly compares the device to Digene's Hybrid Capture 2(hc2) High Risk HPV DNA Test ("the Digene Test"),

although the Digene Test uses a completely different scientific basis to determine in a sample.

c. The denial results in the FDA's over regulation of the device as a cancer test rather than as a test for a common virus, thus requiring unnecessary and costly PMA submission, in violation of the least burdensome provisions of the Food and Drug Administration Modernization Act of 1997 (as codified at 21 U.S.C. §360c(i)(1)(D) and 360c(a)(3)(D)(ii)) and at the expense of public interest.

d. The denial violated the non biased implementation of the risk based medical device classification provisions under 21 CFR § 860.3(c) in that other in vitro devices for the detection of infectious agents that may lead to chronic inflammation leading to cancer with human mortalities higher than that caused by cervical cancer, such as tests for H. Pylori (causing stomach inflammation), have been regulated as class I or II tests by the FDA without requiring PMA submissions. Such inconsistent and asymmetrical implement of the medical device statutes is not in the best interest of public health.

e. Although the portion of the denial based upon FDA's assertion that the device will be used to assess a woman's risk of developing cervical cancer and guide patient management decisions is erroneous, if it were correct, denying class II status is inconsistent with the FDA's decision regarding the classification of MammaPrint® (an in vitro device for the purpose of determining breast cancer prognosis).

m. The portion of the denial based upon the probe design is erroneous because the device does not use a probe; rather, the device uses a process known as PCR (polymerase chain reaction) to replicate HPV DNA for automated DNA sequencing, a technology perfected in the work of the national Human Genome Project research.

r. The portion of the denial based upon the asserted lack of clinical sensitivity and clinical specificity data is inconsistent with the prior approval of similar HPV DNA PCR based amplification methodology for confirming the clinical safety and effectiveness of Gardasil® without such evaluation by clinical sensitivity and clinical specificity data, and the denial provides no reason as to why a method is scientifically acceptable for drug or vaccine evaluation with the results utilized to support clinical safety and effectiveness of the drug or vaccine, but not acceptable for preparing material for clinical tests in monitoring vaccine safety in patients.

JA 8 13. Of these errors, the two Plaintiff finds most disconcerting are (1) that FDA has evaluated the device as a cancer test instead of a test for a virus and (2) that FDA questions the probe design when the device uses primers and does not use probes at all (although other HPV DNA devices currently approved by FDA do use probes, albeit based on different technology).

Regarding evaluating the device as a cancer test – it is simply not a cancer test. FDA has previously agreed: on March 31, 2003, an official FDA News Release (P03 26) from the Commissioner's office stated:

> The FDA today approved expanded use of a laboratory test to detect the presence in women of human papillomavirus (HPV), one of the most common sexually transmitted infections.
>
> The HPV DNA test does not test for cancer, but for the HPV viruses that can cause cell changes in the cervix. If left untreated, these changes can eventually lead to cancer in some women.

As discussed above, for an HPV infection to possibly cause cancer it must be a persistent, high risk type of HPV infection that does not resolve itself, and even then it takes months or years to develop precancer lesions which, if not treated, may lead to cancer in some patients. FDA acknowledges that an HPV infection may exist for months or years before precancer or cancer manifests itself. JA 24. Nonetheless, FDA claims that Plaintiff failed to show clinical sensitivity of the device, claiming: "FDA cannot assess clinical sensitivity, meaning the proportion of individuals who have precancer/cancer who test positive on the HPV

DNA Test." JA 64. This is logically inconsistent: if an HPV infection can exist for years without causing precancer/cancer (if it ever causes cancer), then the one-occasion detection of HPV has no bearing on the existence of precancer/cancer, nor whether the device used to detect HPV correctly detected the existence of precancer/cancer. FDA applies the same faulty analysis to an asserted lack of "specificity." JA 64. The focus on cancer has no scientific bearing on the validity – or sensitivity and specificity – of the device. The proper inquiry into whether the device is a "cancer test" as FDA baldly and repeatedly claims is an inquiry not possible if one looks only at FDA's self-created record.

FDA's focus solely on cancer also leads FDA to make classification of the device more stringent than other devices that screen for infection known to have an eventual link with cancer such as *H. Pylori*, a bacterium known to cause persistent inflammation, ulcers and cancer of the stomach. JA 51. Although FDA's pre-denial analysis claims that *H. Pylori* tests "are not expressly intended for use in cancer screening," FDA does not state the "express" use for such screening. As shown above, neither is Plaintiff's device "expressly intended for use in cancer screening," that is FDA's conclusion. FDA's *official* denial of the petition completely ignores the *H. Pylori* analysis. *See* JA 55-68. Of course, the fact that sunburn may cause melanoma does not permit FDA to over regulate hats. By

focusing only on the potential for cancer, FDA ignores the true purpose of the test as a virology test and requires Plaintiff to meet impossible and illogical standards.

In fact, FDA's denial also ignores the analysis of other agencies of the U.S. Department of Health and Human Services, the parent of the FDA. The Centers for Disease Control and Prevention, also under the umbrella of HHS, held a meeting of the Clinical Laboratory Improvement Advisory Committee in September of 2005. *See* http://wwwn.cdc.gov/cliac/cliac0905.aspx. Dr. Gutman, the author of FDA's petition denial, is an *ex officio* member of the Committee and attended the meeting. There, Ms. Judith Yost (another *ex officio* member) and Ms. Cheryl Wiseman, both from the Centers for Medicare and Medicaid Services (another office under HHS) acknowledged use of molecular testing for human papillomavirus (HPV) to resolve discrepancies in interpreting Pap tests, "but noted HPV testing is a virology test." Again, FDA failed to address this in its administrative record. Whatever the link between HPV and cancer, the device at issue is not a cancer test and should neither be evaluated nor regulated as one.

Regarding the probe design – the device simply does not use probes. The most telling illustration of FDA's error in this regard is FDA's attorney's attempt to conflate the definition of probes and primers in its district court brief, which *post hoc* rationalization is clearly inappropriate. Islander E. Pipeline Co., LLC v. McCarthy, 525 F.3d 141, 166 (2nd Cir. 2008) ("[W]e may not accept appellate

counsel's post hoc rationalizations for agency action. It is well established that an agency's action must be upheld, if at all, on the basis articulated by the agency itself.") (internal quotations omitted). FDA's Memorandum in Support of its motion at pages 26-27 states that: "the term 'probe,' see AR 306, 504, was intended to encompass the 'primers' that are used by Plaintiff's HPV Device." Nothing in AR 306 or 504 mentions primers at all. The Memorandum goes on to say that probes are used to identify DNA targets "for the purpose of replicating the targets," but AR 306, n. 40, states only that probes recognize DNA and says nothing about replication. *See* AR 306.

The glossary of everythingbio.com defines a probe as a "defined nucleic acid (DNA or RNA) that can be used to identify, usually through autoradiography, specific DNA or RNA molecules bearing the complementary sequence." In essence, a probe identifies DNA molecules. In contrast, biology online.org defines a primer as "a short pre-existing polynucleotide chain to which new deoxyribonucleotides can be added by dNA polymerase," "a short sequence (of RNA or DNA) from which DNA replication can initiate." In other words, a primer replicates DNA molecules by PCR. The difference between probes and primers is not apparent in FDA's record, but the need to stretch the definition to cover FDA's mistake shows the need for inquiry outside that record.

These issues are absent from the administrative record and thus require outside evidence. For this reason, even if Plaintiff had not responded to FDA's motion, the district court should have denied the motion. See Maggette v. Dalsheim, 709 F.2d 800, 802 (2nd Cir. 1983). On remand, the district court should permit inquiry into facts outside of the administrative record instead of granting FDA's motion. While it is clear that the first step in judicial review under the APA is review of the administrative record, courts have permitted introduction of evidence from outside the record when the agency has not considered all relevant factors, when the reviewing court simply cannot evaluate the challenged action on the basis of the record before it, or when there has been a strong showing in support of a claim of improper behavior on the part of agency decision makers. National Audubon Soc'y v. Hoffman, 132 F.3d 7, 14 (2nd Cir. 1997). Here, FDA did not consider all relevant factors, including the distinction between probes and primers and the functional differences between the Digene HC2 methodology and *H. Pylori* test intended uses versus the device. The district court cannot evaluate FDA's denial because FDA focused almost exclusively on the cancer aspect of the test rather than the scientific basis for the test. Lastly, FDA simply acted improperly. From the refusal to rule upon the initial petition for reevaluation of Class III status (JA 17), to the delay in ruling on the petition eventually denied, to the focus on cancer, to the failure to allow any comment by or ask any questions of

Plaintiff during the petition process, FDA has shown an unwillingness to deal fairly with Plaintiff.[2] Tummino v. Torti, 603 F. Supp. 2d 519, 543 (E.D.N.Y. 2009) (FDA's failure to make a final decision with regarding to a petition found to be an indication of bad faith.)

The district court erred in granting the motion without inquiring into the basis of FDA's decision. This Court should reverse the district court's decision and either order the petition granted or remand the case for further fact finding.

II. FDA'S DENIAL OF THE PETITION WAS ARBITRARY AND CAPRICIOUS AND SHOULD HAVE BEEN REVERSED BY THE DISTRICT COURT.

FDA's denial of Plaintiff's petition is arbitrary, capricious and an abuse of the discretion delegated to it by Congress because (1) it ignores the current state of the science of DNA testing, (2) it ignores court recognition of this science as legally acceptable, (3) it violates FDA's own statements regarding the type of test being done, (4) it ignores the evidence presented as to safety and efficacy of the device, and (5) it misapplies the standards regarding classification of devices. For

[2] Indeed, FDA even states in its final paragraph of the denial that "This list [of alleged problems with the petition] is not meant to be exhaustive." JA 68. This is either an acknowledgement that FDA did not address all relevant issues in the petition or it is a veiled threat to raise even more objections should Plaintiff answer those in the denial.

these reasons, the denial of the petition should be reversed and the device reclassified as Class II.

This Court reviews the district court's grant of the motion for judgment *de novo*. Patel v. Contemporary Classics of Beverly Hills, 259 F.3d 123, 126 (2nd Cir. 2001).

A. PCR Is Accepted By The United States Courts.

The efficacy and acceptance of PCR is beyond argument, as noted in U. S. v. Morrow, 374 F. Supp. 2d 51, 61, (2005):

> Over the past decade, numerous federal courts in a variety of jurisdictions have analyzed whether the introduction of DNA evidence garnered from the FBI Laboratory's use of PCR/STR analysis comports with the requirements laid down in Daubert. These courts have been virtually unanimous in finding that the use of PCR DNA testing is admissible, and many of these courts have taken judicial notice of the general reliability of such tests. See, e.g., United States v. Wright, 215 F.3d 1020, 1027 (9th Cir. 2000), cert. denied, 531 U.S. 969, 121 S. Ct. 406, 148 L. Ed. 2d 313 (2000); Hicks, 103 F.3d at 846 47; Beasley, 102 F.3d at 1448 (taking judicial notice of general reliability of PCR testing); Shea, 957 F. Supp. at 338 39; Ewell, 252 F. Supp. 2d at 106 (looking specifically at PCR/STR testing and listing twelve state appellate court cases finding PCR/STR DNA testing to be scientifically reliable); United States v. Cuff, 37 F. Supp. 2d 279, 282 (S.D.N.Y. 1999); Gaines, 979 F. Supp. at 1433 36 n.4 (collecting at least twenty state appellate court cases finding PCR DNA testing to be scientifically reliable); Trala, 162 F. Supp. 2d at 351 (looking specifically at PCR/DNA testing); United States v. Lowe, 954 F. Supp. 401, 416 17, 420 21 (D. Mass. 1997) (collecting approximately twenty state appellate court cases finding that PCR testing methodology comports with Daubert). As the district court in Shea explained in 1997,

> although PCR is a relatively new technology, it is based on sound scientific methods and it has quickly become a generally accepted technique in both forensic and non-forensic settings. Perhaps the strongest evidence on this point is the conclusion reached by the National Research Council's Committee on Forensic DNA Science that "the molecular technology [on which PCR is based] is thoroughly sound and … the results are highly reproducible when appropriate quality control methods are followed." NRC II, supra, at 23; see also Mange, supra, at 287 (noting PCR's "widespread and growing applications [in the field of molecular biology]").

B. The Petition To Reclassify The Device Should Have Been Granted Because Plaintiff Proved That The Device Is Safe And Effective For The Detection Of HPV DNA With The Use Of Special Controls As Required By Law And Regulation.

The crux of this case is whether sufficient information exists to establish special controls to reasonably assure the safety and effectiveness of the device so as to classify it as Class II. See 21 U.S.C.A. § 360c(a)(1)(B). As opposed to cases "where the benefits are essentially impossible to determine" because of the complete lack of scientific proof for the device (General Medical Co. v. FDA, 770 F.2d 214, 221 (1985)), the science underlying Plaintiff's device is universally accepted. Plaintiff proved, and submitted the proof to the FDA in its petition, that the device is safe and effective through testing and comparison with an FDA approved test for HPV. The petition should have been granted.

1. Plaintiff Submitted Valid Scientific Evidence Regarding The Safety And Effectiveness Of The Device In Accordance With FDA Regulations.

The safety and effectiveness of the device when used with special controls was proven in the petition as required by 21 CFR §860.7. Plaintiff addressed all of the factors listed for consideration in §860.7(b):

a) The Persons For Whose Use The Device Is Represented Or Intended:

The device is a screening test for sexually active women at risk for infection with HPV. AR 112. There are no risks of overdose, infection, or other dangers related to implanted devices or drugs. Indeed, a patient will likely never come in contact with the device at all.

b) The Conditions Of Use For The Device, Including Conditions Of Use Prescribed, Recommended, Or Suggested In The Labeling Or Advertising Of The Device, And Other Intended Conditions Of Use:

Because of the technical nature of the device, it is to be used only by qualified professionals within state and federal certified laboratories under supervision of a medical director. This is not a device to be placed on a pharmacy shelf and used by an untrained consumer. AR 125.

c) The Probable Benefit To Health From The Use Of The Device Weighed Against Any Probable Injury Or Illness From Such Use:

The benefit is clear – a preliminary identification of HPV DNA with the ability to prepare DNA samples for further specific HPV genotyping to determine

whether persistent HPV infection exists in follow-up repeat testing. AR 125. The potential injury is minimal, if any – the device itself cannot harm the patient, and it is used in conjunction with DNA sequencing for genotyping, and Pap smear cytology examinations (not in lieu of), and never generates a stand-alone diagnosis of disease (AR 111, 114, 117), or even an HPV genotyping, to ensure that a physician's judgment based on all relevant factors is paramount in any patient decision (AR 125). See, infra, discussion of unreasonable risk of injury.

d) The Reliability Of The Device:

Again, the science is unassailable. More convincing, as discussed above, this device when used together with DNA sequencing outperformed the Digene HC2 device, the latest FDA approved for HPV testing. AR 142-148. If false negatives are an issue, as FDA claims, then the device currently approved should be reevaluated. But the device produced fewer false negatives than the Digene test. Reliability is simply not in question.

Because the benefits of the device outweigh the risks when used according to the proper conditions and under a physician's care, the device is safe in accordance with §860.7(d).

Because the device when used together with DNA sequencing provides clinically significant results (indeed, more accurate results than the latest approved

device) in the target population, the device is effective in accordance with §860.7(e).

Simply put, all regulations have been satisfied. The proven scientific basis and the specific relation to an approved test, in addition to the specific, independent reproducibility of the test, prove that the device is safe and effective.

2. FDA's Reasons For Denial Fail.

All of the reasons cited by FDA for denial of the petition fail when viewed against the scientific basis of the device, the proven safety and effectiveness of the device, and the record. FDA's denial is based solely on unsupportable, arbitrary judgments, perhaps due to FDA's failure to understand the science, refer the matter to a panel for review, and its rush to enter a decision after its failure to comply with the statutory time limitations.

a) The Device Is Not A Cancer Test.

As discussed above, the device is simply not a cancer test.

b) Plaintiff's Data Supporting Reclassification Is Sufficient To Prove That The Device Is Safe And Effective.

As shown above, Plaintiff tested the device itself, compared the results to the FDA accepted device, and confirmed the results by DNA genotyping with DNA sequencing. All of the bases for the denial represent either a misunderstanding of the science involved in DNA PCR or a refusal by FDA to acknowledge the basic efficacy of the device.

i. Cross reactivity does not exist in genotyping.

FDA's arguments that no studies were performed for cross reactivity and interfering substances misunderstands PCR technology. In the HPV DNA PCR procedures, "promiscuous" primers are used to amplify the target HPV DNA of numerous genotypes; that is, the primers will bond to any DNA that matches the target ends, even if it is not HPV. Because the primers replicate any DNA with two segments that match the primers, there is a chance that some other types of DNA may be amplified. However, the sizes of these non-specific PCR products are different from those of HPV DNA, and can be readily recognized and excluded by the scientists performing the test. The purpose of PCR amplification is to screen the presence of HPV DNA and to provide presumptive evidence of possible presence of HPV DNA in the sample. This is the sole use of the device: to amplify DNA that is presumptively HPV. Final confirmation of the HPV DNA and its genotype, if detected, depends on additional analytical techniques, the most accurate of which is DNA sequencing, similar to that used in criminal court cases and paternity testing. Because Plaintiff recommends DNA sequencing to be used as the standard technique for validation of the HPV DNA PCR products and for accurate HPV genotyping, relying on the publicly available database of the National Center for Biotechnology Information (the GenBank) maintained by the

National Institutes of Health as reference standard for signature sequence algorithms, cross reactivity is not an issue in using Plaintiff's device.

Similarly, because the device can perform with miniscule amounts of DNA present, interfering substances do not affect the results as significantly as with current probe technology used by other HPV tests currently marketed. In any case, the results of the Plaintiff device are more accurate than those of the currently approved Digene HC2 device (AR 147-148) and should therefore be acceptable to FDA.

ii. Sensitivity of the device was established.

As stated before, the sensitivity of the device was established through comparison with the Digene device. Further, sensitivity was confirmed through testing diluted specimens of known quantity. AR 140. FDA failed in both analyses because FDA required proof of the existence of cancer for positive tests, and such proof is completely irrelevant under FDA's own explanation of HPV. FDA claims that these tests did not mimic "real clinical specimens," although FDA gives no indication of the ability to measure the amount of DNA present in such specimen before amplification. More than 100 genotypes of HPV exist and at least 40 genotypes of them are clinically relevant in the female anogenital area. Each HPV genotype is amplified by different primer pair with different efficiencies. There is no generally accepted standard to measure sensitivity of HPV detection in

clinical specimens because the standard genotypes cannot be decided with general agreement. It is impractical to set 40-100 standards for HPV detection sensitivities. The FDA has not set such a standard for evaluation of HPV DNA testing devices. FDA's other statements in this paragraph have no support whatsoever. What FDA considers "statistically significant" is never stated and simply arbitrary. Testing for all high risk types of HPV is redundant as the issue here is sensitivity of the device and procedure itself, not the specific results of the device.

iii. The device's sensitivity related to women was established.

FDA should recognize that, as the device is intended to detect HPV in vaginal specimens and prepare samples for genotyping by DNA sequencing, the target population is women. Specimens from women were submitted from doctors in and around New Haven, and those specimens were tested. AR 142. FDA has cited no authority, and Plaintiff is aware of none, that shows that HPV is a strictly age-based infection. All sexually active women exposed to HPV infected sexual partners are susceptible to HPV infection. All of the language regarding precancer and cancer further shows that FDA misapplies the current understanding of HPV and its relation to cancer.

iv. FDA's specificity argument simply restates other arguments and ignores the petition.

To the extent that the specificity argument (AR 500) merely restates the sensitivity argument (AR 500) and its focus on cancer, the argument fails for the reasons stated above.

FDA also argues that it cannot identify "the precise degree" of low risk HPV types detected. AR 500. The petition, however, clearly states the types detected, including low risk types. AR 147. Further, this alleged insufficiency could certainly be cured by limiting the authorized use of the device to high risk HPV types. The definition of "high risk" types may be modified as medical science advances. Plaintiff's device is designed to detect all potentially clinical relevant HPV genotypes. The physicians and the epidemiologists will decide which HPV genotypes are of high risk, which may be related to genetic make up of the host as some cited references in the Petition have indicated. Therefore, this "precise" language seems designed to inhibit any serious consideration of the issue by requiring Plaintiff to adhere to an unknown, undefined standard.

v. Genotyping is not related to cancer.

Plaintiff must reiterate that its device only amplifies HPV DNA, and does not perform HPV genotyping which is accomplished by a secondary test, such as DNA sequencing. Again, FDA erroneously conflates HPV with cancer. AR 500-501. Accurate HPV genotyping can be accomplished through the use of DNA

sequencing using the GenBank database maintained by the National Institutes of Health. This identifies the virus at issue, not the presence of or risk for cancer.

vi. Reproducibility has been proven.

FDA engages in pure speculation when it states that the study failed to account for variables in the testing. AR 501. No variables were shown or alleged at any point. Indeed, the entire issue of testing procedure is the subject of the special controls recommended by Plaintiff for the use of the device, discussed below. The test Plaintiff performed was reproduced, and the use of the device by trained, licensed laboratory professional will ensure such procedures are followed.

vii. Stability of the device was established.

Stability of the device over time and at different temperatures was established through testing. The results of the tests were reported. AR 150. Again, FDA has simply chosen to state that Plaintiff failed without providing any reason why.

c) Plaintiff's Controls Are Adequate To Provide Assurances Of Safety And Effectiveness Of The Device.

FDA's assertions that special controls will not suffice to ensure the accuracy of the device are similarly faulty. AR 501-502. The controls reviewed by FDA show that the device will only be used by professionals, thus allaying fears of user error. Warnings that the device should be used only in conjunction with Pap smears and physician oversight further protect against relying too heavily on the

device as the final arbiter of patient treatment. Genotyping will confirm positive results, and this process is clearly understood by the scientific community. False negatives are fewer than with Digene's approved device, so the danger of delayed treatment is greater now than if the device were reclassified. In sum, all of the issues discussed in the prior sections can be addressed with the use of these controls. There is little question as to the safety and effectiveness of the device, and the special controls further ensure it.

d) Sufficient Information Exists To Establish Special Controls Such That The Device Can Be Reclassified As Class II.

In its final argument, FDA claims that insufficient information exists to establish controls to ensure the safety and effectiveness of the device. AR 503. In this FDA makes the same errors as throughout its denial letter.

FDA states that the device may not be effective with actual patients, but only actual patients were used in the study supporting the petition; actual patients and samples therefrom gathered by area doctors. FDA states that the device has not been demonstrated to determine what portion of the patients have cancer, but the device is not a cancer test. FDA continues to ignore the performance of the Digene test compared to Plaintiff's device.

Even while stating that "many reasons" exist as to why the device may not be effective, FDA cites only three:

1. FDA claims that because the device uses a small sample, the device may not work if few cells containing target DNA exist in the sample. This ignores the data submitted with the petition showing as few as 10 copies of DNA are required for a successful test. This alleged defect is also simply curable – require a larger sample. FDA has no basis for believing a simple control as to the sample size will not cure this defect. (Indeed, it seems that the great ability of the device to detect small amounts of DNA is being used against it.)

2. FDA claims that the risk level of each type of HPV is the subject of debate. Why debate about the risks of one type of HPV over another should prevent a device that can detect both types from being used is puzzling. If a physician diagnoses a type of HPV, the physician (not the device) will determine the risk related to that type. It makes no sense that the medical debate about the effect of certain viruses should impede attempts to detect the virus.

3. FDA claims that probe design has not been sufficiently shown. As discussed above, primers, not probes, are used in DNA PCR. This particular mistake is instructive to show that FDA's discretion is being abused because either (a) FDA does not understand the current state of DNA PCR technology or (b) FDA is misapplying the theories applicable to the device for some reason.

CONCLUSION

The district court should have permitted Plaintiff to proceed with the case instead of deciding the case solely based on the record. FDA's record is replete with baseless assertions and illogical statements, and Plaintiff's pleading required facts and analysis from outside the record. Further, the district court should have reviewed these failures and found the denial arbitrary and capricious. This Court should now do so.

Plaintiff requests that this Court reverse the trial court and order FDA to grant the petition or, in the alternative, remand the case to the district court for further fact-finding.

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/s/ Anthony J. Musto
Anthony J. Musto
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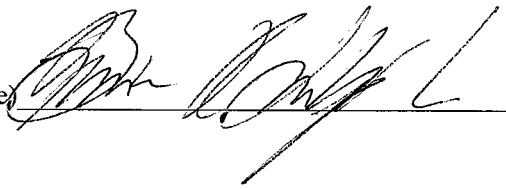
(Your Signature) 

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