SUMMARY MINUTES

OF THE

MICROBIOLOGY DEVICES

PANEL MEETING

OPEN SESSION

March 8, 2002

Gaithersburg Holiday Inn
Gaithersburg, MD

Attendees
Microbiology Devices Advisory Panel Meeting
March 8, 2002

Panel Members

Michael L. Wilson, M.D., Chair
Denver Health Medical Center

Kathleen G. Beavis, M.D.
Cook County Hospital

Laura A. Koutsky, Ph.D.
University of Washington

David T. Durack, M.D., Ph.D.
Industry Representative
Becton Dickinson Biosciences

Stanley M. Reynolds
Consumer Representative
Pennsylvania Department of Health

Panel Consultants

Donald A. Berry, Ph.D.
M.D. Anderson Cancer Center

George G. Birdsong, M.D.
Grady Memorial Hospital

Juan C. Felix, M.D.
Los Angeles County Women's and Children's Hospital

Janine Janosky, Ph.D.
University of Pittsburgh School of Medicine

Valerie L. Ng, Ph.D., M.D.
San Francisco General Hospital

Kenneth L. Noller, M.D.
Tufts University Medical School/New England Medical Center

Frederick S. Nolte, Ph.D.
Emory University School of Medicine

L. Barth Reller, M.D.
Duke University Medical Center

Carmelita U. Tuazon, M.D.
George Washington University Hospital

Melvin P. Weinstein, M.D.
University of Medicine & Dentistry of New Jersey

Panel Discussants

Herschel W. Lawson, M.D.
National Center for Disease Control and Prevention

Elizabeth R. Unger, Ph.D., M.D.
Centers for Disease Control and Prevention

FDA Personnel

Steven I. Gutman, M.D., M.B.A.
Director, Division of Clinical Laboratory Devices
Office of Device Evaluation

Freddie Poole
Panel Executive Secretary

Thomas E. Simms
Sr. Review Scientist, Virology Branch
Division of Clinical Laboratory Devices

Marina Kondratovich, Ph.D.
Mathematical Statistician,
Office of Surveillance and Biometrics

OPEN SESSION

Panel Chair **Michael L. Wilson, M.D.,** called the meeting of the Microbiology Devices Panel to order at 8:37 a.m. and asked the panel members to introduce themselves. Panel Executive Secretary **Freddie Poole** read the conflict-of-interest statement, noting that a waiver had been granted to **Juan Felix, M.D.,** for his unrelated consultant agreement with a firm having a financial interest in the sponsor and that he could participate fully in panel deliberations. The agency took into consideration matters involving **George G. Birdsong, M.D.,** who had current interests in firms at issue that were unrelated to the agenda and determined that he could participate fully in panel deliberations. Ms. Poole noted that **Elizabeth R. Unger, Ph.D., M.D.,** had reported her employer's unrelated involvement with a firm at issue.

Dr. Wilson then stated that the panel's charge was to deliberate on a premarket approval supplement to the Digene High Risk HPV DNA test (the Hybrid Capture II test), a nucleic acid hybridization in vitro diagnostic device for the detection of 13 types of high-risk types of human papillomavirus (HPV) in cervical specimens. The device's modified indications are for use as a general population screening test in conjunction with the Papanicolaou (Pap) smear for women age 30 and older, as an aid to determining the absence of high-grade cervical disease or cancer.

Sponsor Presentation: Digene Corporation

Charles M. Fleischman, President, Digene Corporation**,** began his presentation by stating that the Hybrid Capture 2 device used in conjunction with the Pap smear provides better clinical medicine than the Pap alone and that the device is better at detecting disease than the Pap alone. He emphasized that

they are seeking approval for the device used with the Pap smear for screening women age 30 and older.

Mark Del Vecchio, Director, Regulatory and Clinical Affairs, Digene Corporation, introduced the sponsor's representatives and provided an overview of the major discussion points. Mr. Del Vecchio described the current approved claims for the device and the proposed intended use.

F. Xavier Bosch, Chief, Epidemiology and Cancer Registry, Institut Catala d'Oncologia, Barcelona, Spain, an investigator for Digene Corp., reviewed the scientific literature on the associations between various risk factors and cancer. He stated that HPV DNA has been found in virtually all cases of cervical cancer; that the scientific consensus is that HPV is a necessary, but not sufficient, cause of cervical cancer; that the absence of HPV means lower risk for cervical cancer; and that the presence of HPV means increased risk.

Walter Kinney, M.D., Division of Gynecologic Oncology, TPMG Sacramento, a Consultant to Digene Corp., presented data from an HMO-based study on clinical utility of combining cervical cytology and HPV testing. He noted that because invasive cancer is not an option for an endpoint, CIN2+ was used as the clinically relevant endpoint instead. Patients who tested negative for HPV received reassurance; those testing positive received guidance on follow-up testing and compliance. In his opinion, the study demonstrated that the clinical value of the test outweighs the perceived negatives of having to educate patients about the implications of testing positive for HPV. Dr. Kinney also presented data from other studies, including data from the IARC study, which pooled data from 10 sites outside the United States. He concluded by stating that the additional information that high-risk HPV

testing provides is useful to clinicians in many ways and that in settings in which screening intervals of more than 1 year are recommended, the presence of high-risk HPV in women age 30 and older helps identify patients who might benefit from annual Pap smears.

Attila T. Lörincz, Ph.D., Senior Vice President and Chief Scientific Officer, Digene Corporation discussed the clinical data in support of the sponsor's amended PMA. He described the inclusion criteria for the eight studies selected and stated that all eight studies were conducted under rigorous protocols. He described the target condition, which was histologically confirmed high-grade disease, including cancer. When data were available; CIN2+ was included in the definition of high-grade disease. The clinical goal, he stated, is to identify women at increased risk and to direct appropriate patient management to remove high-grade disease before cervical cancer develops. Dr. Lörincz described the specimen-collection devices and provided details on the Portland/Kaiser study, which he said supports the proposed claim even without the data from the other studies. He presented information on HPV detection using cervical lavage methods, the applicability of the foreign studies to the U.S. population, and other considerations pointing to the strength of the studies. Dr. Lörincz then presented comparisons of the sensitivity data from the eight studies, negative predictive value, and positive predictive value for CIN2+ and CIN3+ endpoints. After noting several potential limitations of the studies—namely, issues involving the collection devices, which are not currently approved for use for HPV—he stated that in all eight studies, HPV as an adjunct to Pap was a more sensitive indicator for cervical disease than Pap alone and produced only a minor reduction in specificity.

Joseph Canner, Biostatistician, Hogan & Hartson LLP, consultant for Digene Corp., presented Digene's statistical analysis plan, which was developed prior to data analysis. Because each study was conducted independently under a different protocol, the decision was made to analyze the studies separately. The success criteria for each study were developed based on two assumptions: (1) that the outcome of interest was cervical disease CIN2+ and (2) that the success criteria were to be applied to the estimates of sensitivity and specificity uncorrected for verification bias. Mr. Canner then described the statistical methodology for analyzing the sensitivity and specificity of the device and presented comparative data from the eight studies.

Next, Mr. Canner presented information on verification bias. He explained that because women are not typically referred to colposcopy, the true prevalence of false and true negatives is unknown. He described four approaches to dealing with verification bias and stated that none is entirely ideal. Finally, he presented data on subsets of patients who tested negative on both tests and were referred (some randomly) to colposcopy for verification. On the basis of the results for the more than 1,500 women who received colposcopy, he stated that the sponsor is confident that verification bias is minimal. Dr. Canner stated that the FDA's statistical review used an overly conservative analysis. He summarized by saying that although Pap sensitivity is highly variable in the eight studies, the combined test provides uniformly high sensitivity. He believes that the data presented constitute valid scientific evidence that provides reasonable assurance of the safety and effectiveness of the Digene device as an adjunct to Pap smear in the evaluation of cervical disease risk.

Dr. Maureen Killackey, Bassett Regional Cancer Program, Cooperstown, NY, and Associate Clinical Professor of OB/Gyn, Columbia University, and a guest speaker for Digene Corp., presented a

clinical perspective on the device. She stated that women and providers need to be educated about the natural history of HPV infection. The combination of HPV and Pap tests can help reassure women about their risk, increase follow-up compliance, and identify women who need frequent screening. The test can also help clinicians avoid inappropriate colposcopy referrals and unnecessary surgery.

J. Thomas Cox, M.D., Director, Gynecology & Colposcopy Clinic, University of California Santa Barbara, presented an algorithm for management of individuals tested by both HPV assays and cytology. He discussed studies in the literature which demonstrate the subjectivity and variability in the reading of Pap smears and stated that adjunctive HPV testing provides clinically meaningful improvement in sensitivity. He summarized the U.S. cervical screening guidelines, and presented a diagnostic algorithm for use in the proposed labeling. He emphasized that the consequence of a false-positive HPV test was more diligent surveillance, not unnecessary colposcopy.

Jonathan Kahan, Hogan & Hartson, Washington, DC, Legal And Regulatory Counsel for Digene Corp., summated that the sponsor was seeking approval for an expanded claim and emphasized that HPV was not a substitute for the Pap test. He summarized the points made by the previous speakers: Adjunctive HPV testing provides a clinically important increase in sensitivity with an acceptable decrease in specificity and is an objective means of identifying women at increased risk of high-grade disease. The data support the sponsor's claim and proposed labeling, and the recommended diagnostic algorithm is consistent with current screening guidelines.

Dr. Wilson then invited the Panel to ask questions of the sponsor.

Panel members asked the Digene representatives for additional information on their rationale for determining that the changes in sensitivity and specificity were appropriate for the device. Sponsor representatives responded that the objective reliability of the HPV test, coupled with the elimination of the consequences of Pap-test false positives, makes the decrease in specificity acceptable. Panel members continued to express concern about the decrease in specificity associated with the HPV test. **Dr. Lörincz** stated that the sponsor had discussed the matter with FDA and felt that the decrease was reasonable.

Kenneth L. Noller, M.D., pointed out that even high grades of CIN can disappear without treatment and asked whether the sponsors had any information on the transiency of additional lesions. **Dr. Cox** responded that anything that improves lesion detection is helpful and that at this point, there is no way to predict which lesions will progress.

Donald A. Berry, Ph.D., asked what women believe when they are Pap negative but HPV positive. **Dr. Killackey** responded that in such cases, patient education is important. **Dr. Cox** added that patient education is improving in light of increased media coverage of HPV and that for most people, HPV infection is transient and has no consequences. **Dr. Felix** noted that if screening is an important prevention strategy, a discrepancy existed between the submission and what the sponsor was proposing with the diagnostic algorithm. **Dr. Cox** replied that the literature gives reassurance that women testing negative on both the Pap and the HPV test are at low risk for cancer and provided additional clarification on the algorithm.

Frederick S. Nolte, Ph.D., noted that the HPV test has a single cutoff point and that no "gray zone" exists around that cutoff. **Dr. Lörincz** replied that the test is highly reproducible and that false positives are rare, so no gray zone is necessary. Dr. Nolte asked whether additional data on quantitative aspects of the test were available for the eight studies, and Dr. Lörincz replied that the sponsor could make the data available.

Panel Discussant

Elizabeth R. Unger, Ph.D., M.D., NCID, Centers for Disease Control and Prevention, provided an overview of human papillomaviruses. She described the typology, high- and low-risk variants, and features of HPV that affect in vitro detection and provided prevalence estimates of HPV-associated disease in the United States. Data indicate that the virus sheds below the limit of detection, but the basal compartment of the epithelium has not been sampled in available studies; no consensus on the definition of persistent infection exists. Regarding the Digene device, Dr. Unger noted that the data indicate good interlaboratory comparison; but the results are not type specific. She also provided comparative information on HPV PCR assays. HPV *in situ* hybridization is the only method that permits direct visualization of the virus in a morphologic context, but the results are technique dependent.

FDA Presentation

Thomas E. Simms, Sr. Review Scientist, Virology Branch, Division of Clinical Laboratory Devices, Center for Devices and Radiological Health**,** presented FDA's analysis of the data based on the proposed indication for use and criteria for screening tests. The goal of the FDA review, he stated, was to evaluate assay effectiveness in the population claimed; however, the eight studies relied on by the

sponsor were not originally designed to evaluate Digene's proposed indication for use and establish performance characteristics. FDA's concerns with the sponsor's data are that not all the studies included the full claimed age range; that the study populations were not consistent with the U.S. population; that one study was a longitudinal study that the sponsor converted to a cross-sectional study for data analysis purposes; that not all women with normal Pap smear results proceeded to colposcopy; that patient follow up was not consistent with U.S. practice; and that study populations were not stratified for low-risk women. Other FDA concerns are that unapproved HPV DNA collection devices were used at three sites; the sites demonstrated differences in cytology readings; and one study was conducted with a less sensitive version of the Hybrid Capture II device. Mr. Simms reviewed the current approved indications for use of the Digene device, and then presented data from the studies in support of FDA's concerns. Finally, he summarized FDA's concerns regarding selection and device bias.

Marina Kondratovich, Ph.D., Mathematical Statistician, Office of Surveillance and Biometrics, Center for Devices and Radiological Health, presented FDA's statistical review. She reviewed each of the eight studies on which the sponsor relied; for each study, she stated the sponsor's estimates of sensitivity and specificity for the study and provided FDA's revised estimates. In FDA's estimation, the increase in sensitivity was affected by verification bias; the sponsor's PMA submission overestimated the increase in sensitivity and decrease in false negatives. The China and Baltimore studies did not demonstrate statistically significant increases in sensitivity when the combination of Pap and HPV tests was used. In addition, the sponsor did not address other biases, such as spectrum bias from differential prevalence and device bias.

Open Public Hearing

Mary F. Mitchell, American College of Obstetricians and Gynecologists (ACOG), presented their recommendations on HPV DNA testing. ACOG's view is that HPV DNA testing lacks specificity. It may be of value in triage of abnormal cervical cytology, but it must be evaluated prospectively in a clinical trial before it can be recommended for routine use.

Linda Alexander, Advocates for Women's Health, spoke in support of the Digene PMA submission, calling HPV screening a "truly primary prevention activity." In addition, HPV testing offers an opportunity to help women understand the implications of Pap test results. The HPV test–Pap smear combination offers an opportunity to improve the status of women's health care. She urged the panel to recommend approval of the PMA.

Wayne C. Shields, Association of Reproductive Health Professionals, also spoke in support of the Digene submission. He stated that approval would allow women to have access to improved technology that can save lives while avoiding unnecessary procedures.

Ms. Poole then read into the record the presentation of **Phyllis Greenberger, MSW,** Society of Women's Health Research, along with letters from **Philip A. Miles, M.D., FACOG, FCAP,** Gyn Path Services, Inc.; **Keith O. Reeves, M.D.; Elinor Christiansen, M.D.,** American Medical Women's Association; and **R. Marshall Austin, M.D., Ph.D.,** Coastal Pathology Laboratories. The presentation and all four letters supported the approval of the Digene submission.

Open Committee Discussion

The panel discussed each question in turn.

Question 1: Does the data submitted support use of HPV DNA testing as a general population screening test in conjunction with Pap smear considering [that] the non-U.S. populations studied showed differences in cervical cancer prevalence and screening practices versus the U.S. population; three sites used collection devices with unestablished performance and one of these an unvalidated matrix; one site defined positives using any positive results up to 3 years after testing; and cytology readings and selection of patients for colposcopy were not standardized across sites?

Laura A. Koutsky, Ph.D., noted that the U.S. population is not homogenous, so having a variety of studies could be advantageous. She also commented on the poor standardization of cytology across sites and observed that because unapproved devices are less sensitive than approved ones, the studies may be more sensitive than indicated and performance will only improve.

Dr. Berry emphasized that guidance for physicians and women needed to be developed if the device was approved. The panel had to consider the practical impact of the device. The issue of verification bias is important for device specificity, and quantification of the bottom line is important.

Dr. Noller observed that women with a positive Pap test often think they have cancer and that the physician needs to spend considerable time reassuring them. An HPV test will only increase anxiety and translate into increased colposcopy exams. One would have to do many colposcopies to pick up one

case of disease—where does one set the bar? It is unclear why Pap smears have to take place annually, but it nevertheless will take a long time to change the interval. **Dr. Felix** concurred and noted that much of the physician–patient relationship is built on the annual Pap test visit. Any extension of the interval would have to involve increased physician and patient education. If managed care settings change their practices, however, general practice might change quickly as well.

Kathleen G. Beavis, M.D., said that expanding the interval is intuitively appealing, but the data do not support it. Implementing widespread HPV screening could lead to increased colposcopies.

L. Barth Reller, M.D., said that the sponsor's studies fell into the category of hypothesis-generating studies. That one could increase or decrease the interval for different populations was plausible but not proved. **David T. Durack, M.D., Ph.D.,** said that although increasing the interval could have benefits, the data do not support it; moreover, expanding the interval is not actually a recommendation of the sponsor. Extension could have unintended consequences.

Dr. Wilson invited a response from Digene to clarify the time intervals. Dr. Kinney said that the current standards are for 1- to 3-year intervals, and the sponsor is not suggesting extension beyond those guidelines. **Dr. Cox** noted that clinicians have not taken advantage of current practice intervals. **Dr. Killackey** said that women can understand that if they are both Pap and HPV negative, they are at low risk and can be screened every 3 years.

Dr. Birdsong responded that if HPV screening were widely implemented, colposcopies would increase because many women will have stress and anxiety and will want to have the procedure to assuage their worries.

Dr. Beavis said that a longitudinal study could demonstrate that the interval could be increased, but the sponsor's studies are snapshots; the question cannot be answered in a single-time study. In response, **Drs. Cox** and **Canner** provided clarification on the study design. **Dr. Kinney** added that the data gave no indication that the sponsor's conclusions are wrong; the Portland study alone is large enough. **Dr. Lörincz** stated that data from the Portland study provided an impressive demonstration of the long-term protective effects of the device's proposed use. Panel members asked various questions for clarification on the study's methodology, which the sponsor representative answered.

Question 2: [Are] Digene's criteria of decreasing false negative rate more than 25% and not decreasing specificity (true negative rate) by more than 10% acceptable to measure the benefit of adding high-risk HPV testing to the normal Pap smear?

Dr. Berry stated that the criteria were not acceptable; one had to consider the implications of the test and its consequences. Sensitivity and specificity are not the only or most relevant characteristics to address. **Dr. Koutsky** noted that positive and negative predictive values vary for different populations, depending on prevalence, and asked what other characteristics could serve as criteria. **Dr. Berry** noted that sensitivity and specificity only address relative, not absolute, risk and benefit.

Dr. Felix said that clinical aspects of sensitivity do not add to its positive predictive value because positive predictive value does not take into account the future risk of disease in HPV positive women. A 25% improvement is reasonable. He would test the hypothesis that sensitivity is higher with the HPV test than without. **Dr. Birdsong** said that the device could serve as an adjunct to cancer screening; the negative predictive value is so good that a 25% increase is reasonable. He had concerns about the decrease in specificity.

The panel members expressed additional concerns over the impact of false positive and false negative readings and the test's positive predictive value. **Dr. Beavis** reminded the panel that the test detects HPV, not the presence of cancer.

Question 3*:* If the panel finds the new indication for use as a general population screening test acceptable, how might the device be labeled and what recommendations should be made for its use, given the different populations and conditions used to derive the data and the nonpoolable nature of the data?

Dr. Felix said that the most important issue involves the consequences of testing positive for HPV—the labeling needs to include guidance for the user. **Dr. Nolte** noted that the labeling goes in the package insert and would be a fairly inefficient way to educate the medical community.

Dr. Reller said that the data are insufficient to provide guidance on clinical practice. Until such data are available, nothing that would change the guidelines should be put into the labeling.

Open Public Hearing

No comments were made.

Industry Response

In response to a comment by **Dr. Nolte**, **Dr. Kinney** provided background on ACOG's recommendations concerning HPV testing. He added that the need for provider education is important but is not a reason to not approve the PMA. **Dr. Cox** said that a prospective clinical study with an endpoint of cancer was not feasible. The issue of unnecessary colposcopies can be handled through education; a greater concern is the 3,000 to 4,000 women who have had screening yet have cancer. Approval of the adjunctive application has public health implications. **Dr. Lörincz** stated that the sponsor's data support the proposed claim for adjunctive use for women age 30 and older. The test is robust, and all studies showed the same trends of improvement. Clinical benefits are that it permits the objective classification of women into low- and high-risk groups. The proposed algorithm will become part of the labeling upon FDA approval. The studies show a remarkable level of congruence, and the decrease in specificity is minor.

Final Recommendations and Vote

Ms. Poole read the voting options for premarket approval applications and noted that **Drs. Beavis** and **Koutsky** were voting members of the panel. She then read a statement signed by the Center Director, David Feigel, M.D., appointing to temporary voting status, **Drs. Berry, Felix, Nolte, Reller, Birdsong**, and **Janosky**.

The panel voted 6-2 to approve the device with the following four conditions:

1. The sponsor should provide specific recommendations for how to use the test in clinical management (including how to interpret results near the cutoff).
2. The sponsor must demonstrate that the recommendations will have a positive impact on clinical outcomes. These conditions could be satisfied by evidence based on data derived from longitudinal studies.
3. The sponsor must develop educational materials to accompany the tests both for laboratory users and clinicians.
4. Postmarketing surveillance must be conducted to assess the impact of the device performance on clinical outcomes.

The Panel Recommended that Conditions 1, 2, and 3 be completed before FDA approval of the device.

Panel members who voted for approval with conditions did so because they felt that the sponsor had not demonstrated safety and effectiveness of the device for the new intended use, but that the test had value as long as it was used in conjunction with specific clinical guidelines. Panel members also indicated that educational materials and postmarket surveillance were important.

Panel members who voted no felt that the conditions were unduly burdensome.

Adjournment

Dr. Wilson thanked the panel, the speakers, and the FDA for their participation and adjourned the session at 4:24 p.m.

I certify that I attended the meeting of the Microbiology Devices Panel on March 8, 2002, and that this summary accurately reflects what transpired.

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Freddie Poole
Panel Executive Secretary

I approve the minutes of this meeting as recorded in this summary.

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Michael L. Wilson, M.D.
Panel Chair

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