DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service P950009

Memorandum

Date SEP 29 1995

From Director, Office of Device Evaluation (HFZ-400)
Center for Devices and Radiological Health (CDRH)

Subject Premarket Approval of Neopath, Inc.
AutoPap® 300 QC System - ACTION

To The Director, CDRH
Through ORA _____

ISSUE. Publication of a notice announcing approval of the subject PMA.

FACTS. Tab A contains a FEDERAL REGISTER notice announcing:

(1) a premarket approval order for the above referenced medical device (Tab B); and

(2) the availability of a summary of safety and effectiveness data for the device (Tab C).

RECOMMENDATION. I recommend that the notice be signed and published.

Susan Alpert, Ph.D., M.D.

Attachments
Tab A - Notice
Tab B - Order
Tab C - S & E Summary

DECISION

Approved _____ Disapproved _____ Date _____

DRAFT

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[DOCKET NO. _____]

Neopath, Inc.; Premarket Approval of the AutoPap® 300 QC System

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing its approval of the application by Neopath, Inc., Redmond, WA, for premarket approval, under the Federal Food, Drug, and Cosmetic Act (the act), of the AutoPap® 300 QC System. After reviewing the recommendation of the Hematology and Pathology Devices panel, FDA's Center for Devices and Radiological Health (CDRH) notified the applicant, by letter on September 29, 1995, of the approval of the application.

DATES: Petitions for administrative review by (insert date 30 days after date of publication in the FEDERAL REGISTER).

ADDRESSES: Written requests for copies of the summary of safety and effectiveness data and petitions for administrative review, to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., Rm. 1-23, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:

Peter E. Maxim, Ph.D.,

Center for Devices and Radiological Health (HFZ-440),

Food and Drug Administration,

2098 Gaither Rd.,

Rockville, MD 20850,

301-594-1293

SUPPLEMENTARY INFORMATION: On February 24, 1995, Neopath, Inc., Redmond, WA 98052, submitted to CDRH an application for premarket approval of the AutoPap® 300 QC System. The device is an automated cervical cytology screening device intended for use in the quality control and rescreening of previously screened Papanicolaou (Pap) smear slides. The AutoPap® 300 QC System is to be used only on conventionally prepared Pap smear slides that have been previously classified as within normal limits (WNL) and satisfactory for interpretation by a screening cytologist. The AutoPap® 300 QC System is not intended to replace the current laboratory slide review processes referred to as "high risk rescreen."

On August 8, 1995, the Hematology and Pathology Devices Panel, an FDA advisory committee, reviewed and recommended approval of the application.

On September 29, 1995, CDRH approved the application by a letter to the applicant from the Director of the Office of Device Evaluation, CDRH.

A summary of the safety and effectiveness data on which CDRH based its approval is on file in the Dockets Management Branch (address above) and is available from that office upon written request. Requests should be identified with the name of the device and the docket number found in brackets in the heading of this document.

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Opportunity for Administrative Review

Section 515(d)(3) of the act, (21 U.S.C. 360e(d)(3)) authorizes any interested person to petition, under section 515(g) of the act, for administrative review of CDRH's decision to approve this application. A petitioner may request either a formal hearing under part 12 (21 CFR part 12) of FDA's administrative practices and procedures regulations or a review of the application and CDRH's action by an independent advisory committee of experts. A petition is to be in the form of a petition for reconsideration under 10.33(b) (21 CFR 10.33(b)). A petitioner shall identify the form of review requested (hearing or independent advisory committee) and shall submit with the petition supporting data and information showing that there is a genuine and substantial issue of material fact for resolution through administrative review. After reviewing the petition, FDA will decide whether to grant or deny the petition and will publish a notice of its decision in the FEDERAL REGISTER. If FDA grants the petition, the notice will state the issue to be reviewed, the form of the review to be used, the persons who may participate in the review, the time and place where the review will occur, and other details.

Petitioners may, at any time on or before (insert date 30 days after date of publication in the FEDERAL REGISTER), file with the Dockets Management Branch (address above) two copies of each petition and supporting data and information, identified with the name of the device and the docket number found in brackets in the heading of this document. Received petitions may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (secs. 515(d), 520(h), ((21 U.S.C. 360e(d), 360j(h))) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10) and redelegated to the Director, Center for Devices and Radiological Health (21 CFR 5.53).

Dated:_____.

_____

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20856

Ms. Patricia Millbank
Vice President, Regulatory Affairs
and Quality Assurance
Neopath, Inc.
8271 154th Avenue N.E., Building H
Redmond, Washington 98052

SEP 29 1995

Re: P950009
AutoPap® 300 QC System
Filed: February 24, 1995
Amended: March 15, April 13, April 19, May 26, June 21, July 12, July 20, July 21, August 11, September 11, September 14, and September 20, 1995.

Dear Ms. Millbank:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the AutoPap® 300 QC System. The AutoPap® 300 QC System is an automated cervical cytology screening device intended for use in the quality control and rescreening of previously screened Papanicolaou (Pap) smear slides. The AutoPap® 300 QC System is to be used only on conventionally prepared Pap smear slides that have been previously classified as within normal limits (WNL) and satisfactory for interpretation by a screening cytologist. The AutoPap® 300 QC System is not intended to replace the current laboratory slide review processes referred to as "high risk rescreen." We are pleased to inform you that the PMA is approved subject to the conditions described below and in the "Conditions of Approval" (enclosed). You may begin commercial distribution of the device upon receipt of this letter.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii), (1) insofar as the labeling specify the requirements that apply to the training of practitioners who may use the device as approved in this order and (2) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

You must submit copies of all advertising in your annual report.

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CDRH will publish a notice of its decision to approve your PMA in the FEDERAL REGISTER. The notice will state that a summary of the safety and effectiveness data upon which the approval is based is available to the public upon request. Within 30 days of publication of the notice of approval in the FEDERAL REGISTER, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the Federal Food, Drug, and Cosmetic Act (the act).

Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

You are reminded that as soon as possible, and before commercial distribution of your device, that you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions concerning this approval order, please contact Peter E. Maxim, Ph.D. at (301) 594-1293.

Sincerely yours,

Susan Alpert, Ph.D., M.D.
Director
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

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I. General Information

Device Generic Name

Cervical cytology device:
Automated image analysis cytology screening device

Device Trade Name

AutoPap® 300 QC Automatic Pap Screener

Applicant's Name and Address

NeoPath, Inc.
8271 154th Avenue N.E.
Redmond, WA 98052

PMA Number

P950009

Date of Panel Recommendation

August 8, 1995

Date of Notice of Approval to the Applicant

September 29, 1995

II. Indications for Use

The AutoPap® 300 QC System is an automated cervical cytology screening device intended for use in the quality control and rescreening of previously screened Papanicolaou (Pap) smear slides. The AutoPap® 300 QC System is to be used only on conventionally prepared Pap smear slides that have been previously classified as Within Normal Limits (WNL) and satisfactory for interpretation by a screening cytologist.

The AutoPap® 300 QC System is not intended to replace the current laboratory slide review processes referred to as "high-risk rescreen."

Intended users are trained cytology laboratory personnel operating under the direct supervision of a qualified cytology supervisor or laboratory director.

Background

The AutoPap® 300 QC System identifies a subset of manually screened negative Pap smears which have been enriched through computer selection for false negative slides. A 10 percent manual screening of this enriched subset will identify up to 50 percent of false negatives when compared to a 100 percent manual rescreen. This compares to the expected identification

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of only 10 percent of false negatives by a completely random 10 percent manual review.

Cancer of the Uterine Cervix

Cancer of the uterine cervix is preceded by a precancerous, more frequently curable stage that progresses without symptoms over a period of years until it reaches an invasive stage. Treating uterine cervical cancer after it has reached the invasive stage becomes more difficult and expensive, and may not be successful. In 1993, approximately 4,400 women died of cervical cancer in the United States. Almost all deaths due to cervical cancer could be prevented with early-stage detection and treatment.[1]

The Pap Smear Test

The Pap smear test, developed in the 1940s by Dr. George N. Papanicolaou, is a screening procedure for the early detection of precancerous and cancerous conditions of the uterine cervix. About 90% to 95% of all Pap smears are initially determined to be normal by cytotechnologists in the laboratory.[2] Regulations promulgated under the Clinical Laboratory Improvement Amendments of 1988 ("CLIA") require a minimum of 10% of all cases judged normal in the cytotechnologist's initial review to be rescreened by another experienced cytotechnologist as a quality control measure.

Despite the acknowledged success of the Pap smear test, certain limitations in the current method of human Pap smear review can adversely affect the accuracy of the laboratory. As a result, Pap smear analysis is subject to a highly variable false negative rate (the percentage of abnormal smears classified as normal divided by the total of abnormal slides). In certain laboratories, this rate may exceed 30%.[3]

III. Device Description

The AutoPap® 300 QC System increases the prevalence of false negatives in selected QC samples when compared to the best possible performance of random selection.[4] The results reported in the PMA show that the AutoPap® 300 QC System provides up to a 5-fold improvement over a 10% random selection method.[5]

The AutoPap® 300 QC System is an automated cytology rescreening device that uses high-speed video microscopes, image interpretation software, and specially designed field-of-view (FOV) computers to recognize, analyze, and classify cells within the complex images on a Pap Smear. The device produces a report that identifies a sample of slides highly enriched with false negative slides for quality control manual rescreening.

This device classifies each successfully processed slide into one of two groups: No Review (no evidence to recommend further human review) or QC Review (further human review recommended; specimen is potentially abnormal or unsatisfactory).

Slides that are not processed successfully are classified as *Review*. The tray report will provide the reason for failure to process and will indicate whether the problem can be repaired so that the slide can be rerun through the System after the problem has been corrected. If the laboratory identifies a subset of slides that cannot be repaired and rerun through the device, it is recommended that the laboratory conduct its usual procedure for routine QC selection for those slides.

The core technology consists of an integrated high-speed video microscope to acquire images, specialized image-interpretation software to accurately analyze images and classify slides, and an FOV computational system to run the software at high speed.

A. Operational Flow

The AutoPap® 300 QC System is designed to process conventionally prepared Pap smears that are stained and preserved under glass coverslips by the laboratory. Each slide is labeled with a slide barcode label and loaded into a slide tray. The trays are then placed into the AutoPap® 300 QC System, which then automatically analyzes the slides.

After loading the slide trays into the AutoPap® 300 QC System, a physical check of the slide is made and the slide barcode label is read.

The AutoPap® 300 QC System then scans the slide and analyzes it at low power (4x). Next, prioritized high-power 20x fields-of-view on the slide are examined in detail. Checks are incorporated along the way to make sure that the slide and specimen are adequate for device analysis.

If, during this stage, any of the characteristics of the slide are determined to be outside of the acceptable range of performance for the AutoPap® 300 QC System, the slide is determined to be "not suitable for scanning."

Once the slide has successfully passed the scanning stage, summary scores are computed for the Pap smear, including a measure of the suitability for algorithm analysis, a quality control score, and adequacy measures of the squamous and endocervical components for the slide. The endocervical score is reported only as supplementary information and provides only the endocervical adequacy status for the slide. It does

not change the final outcome for the slide, (*QC Review* vs. *No Review* decision).

Slide and instrument data are reported to the AutoPap® 300 QC Workstation during processing. The final processing results may be obtained after the completion of the system integrity check for each tray. At that time, the processing report may be printed for each tray. The report identifies the Pap smears for which manual QC rescreening is recommended.

B. *High-Speed Video Microscope*

To facilitate the capture of high-quality images, a high-speed video microscope, consisting of an integrated mechanical/optical system with a custom microscope and video cameras, captures and digitizes images from a Pap smear. The camera system scans the Pap smear in a continuous, systematic motion. The Pap smear is illuminated by high-intensity, narrow-band light from a strobe that enhances image contrast and freezes each image without interrupting the motion of the Pap smear.

The mechanical/optical system is controlled by an image capture and focus module that incorporates specialized integrated circuits and software. This module calibrates the image acquisition system, automatically focuses the system to obtain diagnostically relevant information and adjusts for the non-uniform characteristics of a conventional Pap smear. The image capture and focus module also digitizes images, evaluates image quality, decides whether to accept or reject the image for analysis, and identifies the location of a rejected image for a repeat scan.

C. *Algorithm Software and Slide Classification Method*

The AutoPap® 300 QC System uses a statistical classification procedure to determine which Pap smears should be reviewed. With a statistical classifier, the key elements of the process (features to be measured, thresholds to apply and the disposition of the slide) are all developed under direct human-supervision with the goal of correctly sorting objects into recognizable classes

The NeoPath approach is implemented in hardware-assisted, image-interpretation software. The image-interpretation software developed by NeoPath integrates a series of image-interpretation algorithms that examine slide images to select and analyze those that are the most relevant indicators of abnormality

An image-interpretation algorithm is a multiple-step process that classifies an object or collection of objects based on shape, structure, optical density and other visible characteristics. The process executed by the image interpretation software consists of five steps:

1 Selecting images from a slide
2 Segmenting the images into objects
3 Measuring object features
4 Classifying objects
5 Classifying the slide

Selection of Images

By analyzing images from a low-magnification scan of the full coverslip area of the slide, algorithms first identify the areas most likely to contain cellular material of diagnostic significance. This information then guides the mechanical/optical system to a separate high-magnification scan of the locations of greatest diagnostic interest. The AutoPap® 300 QC System accumulates and stores information gathered in these first steps for later use in the slide classification process.

Segmentation Into Objects

The AutoPap® 300 QC System locates and segments the well-defined cells in each image into objects; while excluding from further analysis poorly defined and overlapping objects as well as obvious artifacts (blood, mucus, dust particles and similar matter).

Measurement of Object Features

Once objects, or groups of objects, are isolated from other elements of the image, algorithms measure over 100 features from each object. "Features" are characteristics of the objects that independently, or in combination, provide effective discrimination among normal cells, artifacts and abnormal cells. The algorithms discriminate on the basis of five general categories of features:

Density features	Measures of the optical density of various portions of the cell, such as the cytoplasm and nucleus, and the ratios of these densities to each other.
Texture	A localized measure of optical density variation.
Size feature	The physical areas of the segmented objects and their ratios to each other.

Shape features	Differentiation of cell types used to discriminate among overlapping objects.
Context	Comparisons of an object to its surroundings and the proximity of objects to each other.

Classification of Objects

A series of algorithms classifies objects contained in the images. Classification of the detected objects is accomplished based on the measured features. Each classification algorithm contains multiple stages that handle easily identifiable objects first, then increasingly difficult objects by adding more features at each level of classification.

Three separate algorithms are used to analyze the cells and cell groupings that could indicate abnormality: the single-cell algorithm, the group algorithm, and the thick-group algorithm.

An "anomaly likelihood" value is computed at various steps of the classification process in which predefined thresholds are applied to provide "alarms," which identify objects that have a higher likelihood of being abnormal cells. The results of the three algorithms are integrated to achieve classification accuracy.

Classification of the Slide

Finally, all the gathered and analyzed information is compiled in a series of scores that are used to classify the slide for quality control purposes (*QC Review* or *No Review*). Other algorithms evaluate the suitability of the slide for machine processing (quality of staining, quantity of cells, presentation of material on the slide, and image quality) and determine the probable presence of certain important cellular material.

D. Field-of-View Computer

Image-interpretation algorithms are implemented in computer programs that must be executed by a high-speed computing system. These algorithms must be performed for each Pap smear image, which requires computing power that was largely unavailable until recently. To address this requirement, the Applicant developed FOVs, specialized field-of-view image-processing computers. FOVs have image processors that contain application-specific integrated circuits and other processing components. The execution speed of the Applicant's image-interpretation software is accelerated through the use of this special-purpose hardware.

FOVs can be linked to run in parallel. The Applicant's current configuration for the device contains 15 FOVs.

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IV. Alternative Practices and Procedures

Currently, laboratories perform this quality control function by removing a random sample of slides from the population classified as normal. The limitation of this method is that it can produce only a small percentage of the false negative slides remaining in the slide population. The proportion of false negatives detected will be equal to the sample size selected (that is, a 10% random sample size can produce only 10% of all available false negative slides).[6]

The primary claim for the AutoPap® 300 QC System is that the device increases the prevalence of false negatives in selected QC samples when compared to the best possible performance of random selection.[7]

V. Marketing History

The Applicant has begun marketing the device in Canada and in Australia. The AutoPap® 300 QC System has not been removed from marketing for any reason relating to the safety and effectiveness of the device.

VI. Adverse Effects of the Device on Health

There are no known direct risks to safety or health caused by, or related to use of, the device. However, cytologic screening errors may result in delayed treatment for precancerous changes. This may be especially pernicious for women who, for one reason or another, do not undergo routine Pap smear testing at the recommended intervals. A false negative smear report for these women may delay diagnosis and allow the disease to progress.

VII. Summary of Studies

A. Reports of Nonclinical Studies

Nonclinical studies were conducted from 1988 through January of 1994. These studies were designed to develop, analyze, and improve the design of the AutoPap® 300 QC System.[8]

During this development effort, many prevalence studies were conducted to better understand the nature of the analysis problem. Significant testing was conducted to determine the requirements for abnormal cell sensitivity, the requirements for the image analysis algorithm, and advanced methods for image collection. Several studies

were conducted to characterize the interactions between the algorithms, software, and opto-mechanical systems. Additional evaluations of the various algorithm modules helped determine the acceptance ranges in focus, prevalence of bubbles and other obscuring matter, and slide thickness.

B. *Reports of Preclinical Studies*

Several preclinical studies were conducted during late 1993 and the first half of 1994. The purpose of these studies was to gather estimates of the performance of the AutoPap® 300 QC System and to determine the validity of the protocols developed to test intended use.[9]

Several thousand slides were processed and analyzed, providing information regarding the performance of the software technology, the reliability of the hardware, and the ability of the laboratories to follow the protocol design. The protocols evaluated during these preclinical studies provided data to finalize the protocols used in the Clinical Evaluation and Sensitivity Studies, discussed below. These preliminary tests provided preliminary data regarding estimates of sensitivities to abnormal slides as well as yield and sort rate information.

C. *Reports of Clinical Studies*

Since laboratories currently use a random selection process as the primary method to choose this quality control subset, the claim of improvement for the AutoPap® 300 QC System is as follows:

> The AutoPap® 300 QC System significantly increases the prevalence of false negatives in selected QC samples when compared to the best possible performance of random selection.[10]

To establish this primary claim, several carefully designed clinical trial experiments were conducted to evaluate the performance of the device in a wide range of operating environments. (There were six individual clinical studies performed, each of which is described in the following sections.) During clinical studies, the AutoPap® 300 QC System demonstrated up to a 5-fold improvement over a 10% random selection method.[11]

C.1 Sensitivity — The Historical Sensitivity Study (HSS)

This study used large sample sizes (up to 100) of archived abnormal slides: AGUS, LSIL, HSIL, detected cancer (squamous, glandular, and extrauterine) and detected false negative slides. Each abnormal slide also required a normal matched control slide. The slides dated from approximately May 30, 1994, back as far as January 1, 1993.

All six clinical sites conducted this study. The total number of slides selected for review was 5,313. The total number of slides submitted for processing was 4,432. The total number of slides that qualified for use in the analysis was 3,589.[12]

The data derived from processing these large samples of archived slides demonstrate that the AutoPap® 300 QC System has significant sensitivity to all tested categories of abnormal slides.[13] That is, the System is able to correctly categorize (as *QC Review* or *No Review*) large samples of abnormal slides within each of the diagnostic categories tested: AGUS, LSIL, HSIL, and cancer.

C.2 Sensitivity — The CAS Evaluation

The second sensitivity study sample population was derived from the more recent population of detected positive slides and the detected false negative slides that were received and diagnosed by each clinical study site during the course of the Clinical Evaluation Study (ASCUS, AGUS, LSIL, HSIL, cancers, and detected false negatives). Each selected abnormal slide required a normal matched control slide.

All six clinical sites conducted this study. The total number of abnormal and WNL slides selected for review was 3,924. The total number of slides submitted for processing was 3,251. The total number of slides that qualified for use in the analysis was 2,584.[14]

The data derived from processing these current, or more recent, abnormal slides further demonstrate that the AutoPap® 300 QC System has significant sensitivity to all tested categories of abnormal slides.[15]

That is, the System is able to correctly categorize (as *QC Review* or *No Review*) abnormal slides within each of the diagnostic categories tested: ASCUS, AGUS, LSIL, HSIL, and cancer.

C.3 Sensitivity Studies Results

- Tables 1 to 2 summarize the sensitivity evaluation results for the three runs of the Historical Sensitivity Study (HSS) at both a 10% and 20% QC review rate. As shown by the close similarities in

sensitivity estimates from all runs, it is evident that the System shows very little effect of imprecision on the clinical classification sensitivity to disease.[16]

- Tables 3 and 4 show the sensitivity, at both a 10% and 20% QC review rate, to abnormal slides from the Current Archive Sensitivity (CAS) study.[17]

- Table 5 shows the overall sensitivity, at a 10% QC review rate, to abnormal slides processed during the Current Archive and Historical Sensitivity studies.[18]

- Table 6 shows a subset analysis of the cancer category of slides from the Historical Sensitivity Study further subclassified by type, and provides the sensitivity, at a 10% QC review rate, to each subclassification of disease.[19]

- Table 7 shows the sensitivity, at a 10% QC review rate to biopsy-confirmed HSILs and cancers (data derived from University of Rochester and Kyto Diagnostics, L.P.). Note that the demonstrated sensitivity produces a 7.7 times improvement over a 10% random selection method.[20]

Table 1 Combined HSS Sensitivity Table — Global 10% QC Review Rate

						Matched
Site 1	Run 1	45.0%	67.4%	84.7%	100.0%	16.5%
	Run 2	48.1%	72.0%	86.2%	100.0%	14.8%
	Run 3	43.6%	72.7%	87.1%	100.0%	16.3%
Site 2	Run 1	33.3%	62.2%	79.0%	86.5%	13.5%
	Run 2	36.7%	54.4%	80.5%	85.0%	12.3%
	Run 3	33.3%	57.6%	84.0%	87.8%	15.6%
Site 3	Run 1	60.0%	68.3%	90.4%	66.7%	34.2%
	Run 2	50.0%	75.7%	95.5%	75.0%	32.2%
	Run 3	40.0%	68.5%	92.2%	75.0%	27.5%
Site 4	Run 1	45.9%	68.7%	87.7%	61.5%	13.3%
	Run 2	52.8%	71.2%	83.6%	53.1%	11.0%
	Run 3	41.9%	66.7%	91.2%	57.1%	13.8%
Site 5	Run 1	N/A	46.2%	70.3%	50.0%	7.6%
	Run 2	N/A	37.2%	74.3%	50.0%	6.7%
	Run 3	N/A	42.9%	68.7%	100.0%	7.1%
Site 6	Run 1	34.4%	60.5%	88.6%	71.1%	10.4%
	Run 2	32.6%	62.9%	84.2%	72.7%	10.8%
	Run 3	30.7%	54.9%	84.8%	69.0%	10.5%

1 Review Rate: Average percent identified as *QC Review* at each laboratory using the global 10% QC review rate.

Table 2 Combined HSS Sensitivity Table — Global 20% QC Review Rate

						Matched
Site 1	**Run 1**	60.0%	84.3%	92.9%	100.0%	31.0%
	Run 2	65.4%	84.9%	89.7%	100.0%	28.5%
	Run 3	60.3%	85.7%	92.9%	100.0%	28.9%
Site 2	Run 1	46.7%	81.1%	95.1%	90.4%	31.4%
	Run 2	50.0%	77.8%	93.1%	95.0%	31.4%
	Run 3	54.2%	71.8%	92.6%	91.8%	28.5%
Site 3	Run 1	60.0%	85.7%	100.0%	100.0%	56.1%
	Run 2	75.0%	87.1%	98.5%	100.0%	51.0%
	Run 3	60.0%	89.0%	96.9%	100.0%	51.0%
Site 4	Run 1	67.6%	85.1%	94.7%	84.6%	34.8%
	Run 2	72.2%	79.5%	95.1%	75.0%	30.1%
	Run 3	64.5%	82.6%	93.0%	71.4%	27.5%
Site 5	Run 1	N/A	66.2%	81.1%	100.0%	15.9%
	Run 2	N/A	60.3%	82.4%	100.0%	17.2%
	Run 3	N/A	57.1%	80.6%	100.0%	17.5%
Site 6	Run 1	46.9%	72.1%	94.3%	76.3%	17.4%
	Run 2	41.3%	77.5%	93.0%	78.8%	20.3%
	Run 3	38.6%	74.4%	91.3%	72.4%	18.1%

1 Review Rate: Average percent identified as *QC Review* at each laboratory using the global 10% QC review rate.

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Table 3 CAS Sensitivity at Global 10% QC Review Rate

	ASCUS	AGUS	LSIL	HSIL	CANCER	Matched Control Review Rate[1] NORMAL
Site 1	34.5%	0.0%	68.3%	83.3%	100.0%	8.6%
Site 2	38.7%	66.7%	54.3%	82.4%	0.0%	14.1%
Site 3	62.9%	N/A	81.0%	92.7%	100.0%	38.7%
Site 4	41.2%	0.0%	53.3%	N/A	N/A	7.4%
Site 5	15.0%	N/A	36.9%	71.4%	0.0%	6.1%
Site 6	50.0%	25.0%	71.1%	81.4%	100.0%	17.5%
Overall Sensitivity (excl. Site 3[2])	36.1%	27.3%	60.0%	80.2%	62.5%	11.3%
95% Conf. Interval	29.5–43.1%	10.7–50.2%	55.1–64.8%	74.0–85.5%	24.5–91.5%	9.3–13.6%

1 Review Rate: Average percent identified as *QC Review* at each laboratory using the global 10% QC review rate.

Table 4 CAS Sensitivity at Global 20% QC Review Rate

	ASCUS	AGUS	LSIL	HSIL	CANCER	Matched Control Review Rate[1] NORMAL
Site 1	40.2%	40.0%	85.4%	91.7%	100.0%	18.8%
Site 2	58.1%	83.3%	77.1%	94.1%	0.0%	37.0%
Site 3	83.7%	N/A	94.8%	100.0%	100.0%	56.9%
Site 4	60.8%	0.0%	73.3%	N/A	N/A	19.1%
Site 5	25.0%	N/A	57.1%	81.0%	0.0%	9.5%
Site 6	75.0%	37.5%	79.9%	83.1%	100.0%	30.0%
Overall Sensitivity (excl. Site 3[2])	49.3%	45.5%	75.6%	87.1%	62.5%	22.5%
95% Conf. Interval	42.2–56.3%	24.4–67.8%	71.2–79.7%	81.7–91.4%	24.5–91.5%	19.8–25.5%

1 Review Rate: Average percent identified as *QC Review* at each laboratory using the global 10% QC review rate.

Table 5 Sensitivity to Abnormal Slides by Diagnostic Category
Current Archive Study (CAS) and Historical Sensitivity Study (HSS)
10% QC Review Rate, % Sensitivity, (N)

	ASCUS	AGUS	LSIL	HSIL	CANCER
CAS	36.1% (205)	27.3% (22)	60.0% (410)	80.2% (202)	62.5% (8)
HSS	N/A	39.5% (243)	60.9% (412)	82.1% (385)	79.1% (139)

Table 6 Sensitivity to Subset of Cancer Slides
10% QC Review Rate, % Sensitivity, (N)

Squamous CA[1]	AdenoCA NOS[2]	Malignant NOS	Endocervical AdenoCA	Endometrial AdenoCA	AIS[3]	Al Can Sli
91.3% (80)	52.6% (19)	40.0% (5)	100.0% (3)	66.7% (15)	58.8% (17)	77.7 (13

1 CA: Carcinoma
2 NOS: Not otherwise specified (specimen contains cellular evidence of adenocarcinoma but unable to further subclassify as to site of origin)
3 AIS: Adenocarcinoma in situ

Table 7 Sensitivity to Subset of Biopsy-Confirmed HSIL and Cancer Slides
10% QC Review Rate

	No. of Biopsies	No. of Biopsies Confirmed	Confirmed Biopsies Called "QC Review"	Sensitivity
HSIL	60	51	43	84.3%
Cancer	35	33	22	66.7%
Total	95	84	65	77.4%

C.4 Precision — 32 Slide Standardized Set

This was a Multiple-Run Study to estimate the ability of the System to obtain consistent results when processing a known set of 32 well-characterized slides up to 30 times (intra-instrument) and to estimate the levels of performance obtained between instruments by processing this set on three separate Systems (inter-instrument). This study was conducted on three (3) Systems located at the University of Rochester (UR), MetPath, and NeoPath.[21]

The results included in the PMA confirm that the repeatability of the instrument in calling a slide *QC Review* or *No Review* is consistent from system to system (inter-instrument repeatability) and within each tested system (intra-instrument repeatability).[22]

C.5 Precision — Multi-Run HSS

This was a Multiple-Run Study using the sample population selected during the Historical Sensitivity Study (AGUS, LSIL, HSIL, detected false negatives, cancer, and the normal matched controls). It was designed to provide additional measures of the performance of the device on a representative population of abnormal slides obtained from each instrument (intra-instrument).

All six clinical sites conducted this study. The total number of slides selected for the study was 5,313.[23] The total number of successful processing runs was 13,229. The total number of slides that qualified for use in the analysis was 10,674.[24]

The results included in the PMA demonstrate that the instrument produces essentially equivalent sensitivity estimates when repeatedly processing large sets of abnormal slides. The data presented illustrates a high degree of between-run agreement overall on abnormal slides. Fisher's 2 × 2 Exact test is used as the statistical test to make the comparison that the *QC Review* and *No Review* rate is consistent within each machine and from machine to machine.[25]

C.6 Precision Studies Results

Table 8 compares three different machines, and for each pairwise comparison, tests the hypothesis that they are the same with p-values.[26] NA indicates that a slide did not have any data available for at least one of the two machines being compared; an asterisk (*) indicates that the review rate was perfectly 0 or 1 (always called *QC Review* or *No Review*) for both machines being compared. The *QC Review* and *No Review* decision is determined by a threshold of 0.386. If an alpha of 0.01 is used for the test, then the null hypothesis of between-site, review-rate consistency will be accepted when the p-values are greater than 0.01.

Table 9 presents the review rate for each lab and for each slide. The diagnosis for each slide is shown in the far right column.[27]

Table 8 Fisher's 2 x 2 Exact Test

	NeoPath	NeoPath	MetPath	
940006439	*	*	*	Normal
940006443	*	*	*	Normal
940006464	*	*	*	Normal
940006467	*	*	*	Normal
940006472	*	*	*	Normal
940006473	*	*	*	Normal
940006476	*	0.474	0.482	Normal
940006487	1	1	0.499	Normal
940006489	*	*	*	Normal
940006492	*	*	*	Normal
940006493	*	*	*	Normal
940006497	N/A	N/A	0.464	Normal
940007379	*	0.455	0.455	ASCUS
940007381	0.483	1	*	ASCUS
940007409	*	0.434	0.434	ASCUS
940007410	1	1	0.444	ASCUS
940007416	*	*	*	ASCUS
921011542	*	N/A	NA	AGUS
940006420	*	*	*	LSIL
940006425	*	*	*	LSIL
940006428	*	*	*	LSIL
940006430	*	*	*	LSIL
940006436	*	*	*	LSIL
940006390	*	*	*	HSIL
940006393	N/A	N/A	*	HSIL
940006397	*	*	*	HSIL
940006398	N/A	*	N/A	HSIL
940007261	N/A	*	N/A	HSIL
921011561	*	*	*	HSIL/CIS[1]
921011562	*	*	*	HSIL/CIS
921011565	*	*	*	HSIL/CIS
921011574	N/A	N/A	N/A	SquamCarc

3 CIS = Carcinoma in situ

Table 9 QC Review/No Review Rates for Each Slide at Each Lab and for Overall

	QC Review					
940006439	No Review	100%	100%	100%	100%	
940006443	No Review	100%	100%	100%	100%	
940006464	No Review	100%	100%	100%	100%	
940006467	No Review	100%	100%	100%	100%	
940006472	No Review	100%	100%	100%	100%	
940006473	No Review	100%	100%	100%	100%	
940006476	No Review	100%	100%	96%	99%	
940006487	No Review	97%	93%	100%	96%	
940006489	No Review	100%	100%	100%	100%	
940006492	No Review	100%	100%	100%	100%	
940006493	No Review	100%	100%	100%	100%	
940006497	No Review	NA	100%	96%	98%	
940007379	QC Review	100%	100%	96%	99%	
940007381	QC Review	97%	100%	100%	99%	
940007409	QC Review	100%	100%	96%	99%	
940007410	QC Review	97%	100%	96%	98%	
940007416	QC Review	100%	100%	100%	100%	
921011542	QC Review	100%	100%	NA	100%	
940006420	QC Review	100%	100%	100%	100%	
940006425	QC Review	100%	100%	100%	100%	
940006428	QC Review	100%	100%	100%	100%	
940006430	QC Review	100%	100%	100%	100%	
940006436	QC Review	100%	100%	100%	100%	
940006390	QC Review	100%	100%	100%	100%	
940006393	QC Review	NA	100%	100%	100%	
940006397	QC Review	100%	100%	100%	100%	
940006398	QC Review	100%	NA	100%	100%	
940007261	QC Review	100%	NA	100%	100%	
921011561	QC Review	100%	100%	100%	100%	H
921011562	QC Review	100%	100%	100%	100%	H
921011565	QC Review	100%	100%	100%	100%	H
921011574	QC Review	NA	100%	NA	100%	Sc

1 CIS = Carcinoma in situ

C.7 *Accuracy — The Clinical Evaluation Study (CES)*

The Clinical Evaluation Study (CES) was designed to compare the effectiveness of current quality control practices in a cytology laboratory to the effectiveness of the AutoPap® 300 QC System in a quality control application. The AutoPap® 300 QC System was operated, as nearly as possible, in a manner similar to that recommended for routine laboratory use.

The objective of the CES was to test the hypothesis that the AutoPap® 300 QC System was capable of providing a higher proportion of false negative slides for quality control review than can be achieved by a random selection method. This hypothesis was evaluated over a range of possible options for quality control review rates (10%, 15%, 20%, etc.) to provide information regarding expected performance of the device at various operating points.

A 100% manual clinical rescreen of all processed slides was used in this study. This design ensured that the site personnel were effectively masked and enhanced the probability of detecting the false negative slides present within the entire study population.

All six clinical sites conducted this study. The total number of slides initially enrolled in the study was 23,099. The total number of slides actually submitted for processing on the device was 18,777. The total number of slides that qualified for use in the analysis, after exclusions and other limitations, was 14,914.[28]

For the CES described in this section, three levels of false negative designations were used, and the relative performance of the AutoPap® 300 QC System compared to a random selection method was evaluated for each successive level of false negative designation. The definition of a false negative is a slide that is actually abnormal (either inadequate for review or indicative of disease) that is incorrectly screened by the initial cytotechnologist and classified as WNL (and adequate for review).

For every slide selected for evaluation in the CES, a 100% manual clinical rescreen (CR) was performed on those slides. Thus, each slide in the CES had an original

manual screen diagnosis that was required to be Within Normal Limits (WNL), and subsequently, a second manual screening diagnosis used for the study.

In the study, each false negative also was reviewed by an Internal Discrepancy Panel (IDP) of study site personnel to resolve the differences (in most cases), as well as an External Discrepancy Panel (EDP) of independent pathologists.

C.8 CES Study Results

Discussion of the results of these three separate reviews of false negative slides is used to compare the instrument to what can be expected for a standard QC rescreen process in the identification of false negatives. Tables 10 to 15 summarize the results of the CES for both the population of all false negative slides as well as for the subset of false negative slides having a severity of LSIL and above.[29] The tables present data at each level of review for the false negative designation (CR, IDP and EDP) at 10% and 20% QC review rates.

The 95% confidence limits on the estimated sensitivities in the tables were also calculated. These calculations demonstrated that all of the observed sensitivities, for both total false negatives and LSIL+ false negatives, were significantly greater than the results for the three comparative random selection percentages.[30]

Table 10 CES Study Results (CR review rate and sensitivity %) at 10% QC Review Rate

	Site 1	Site 2	Site 3	Site 4	Site 5	Site 6	All sites excl. Site 3[1]
Normal Review rate[2]	11.2%	11.8%	37.2%	9.4%	6.1%	19.3%	11.8%
All FNs[3]	29.3%	26.6%	60.5%	37.5%	32.1%	25%	29.3%
All FN-LSIL+[4]	70%	61.9%	N/A	33.3%	35.7%	50%	47.4%

1 Site 3 is excluded from overall results due to incompatibility of staining procedure with the device.
2 Review Rate: Average percent identified as *QC Review* using the global 10% QC review rate.
3 All FNs: Includes the diagnostic categories of ASCUS, AGUS, LSIL, HSIL and Carcinoma.
4 All FN-LSIL+: Includes the diagnostic categories of LSIL, HSIL and Carcinoma.

Table 11 CES Study IDP Sensitivity Results at 10% QC Review Rate

	Site 1	Site 2	Site 3	Site 4	Site 5	Site 6	All sites excl. Site 3[1]
Normal Review rate[2]	11.2%	11.8%	37.2%	9.4%	6.1%	19.3%	11.8%
All FNs[3]	33.3%	48.1%	58.6%	25.0%	36.3%	20.0%	36.4%
All FN-LSIL+[4]	100.0%	57.1%	100.0%	33.3%	29.7%	50.0%	38.6%

1 Site 3 is excluded from overall results due to incompatibility of staining procedure with the device.
2 Review Rate: Average percent identified as *QC Review* using the global 10% QC review rate.
3 All FNs: Includes the diagnostic categories of ASCUS, AGUS, LSIL, HSIL and Carcinoma.
4 All FN-LSIL+: Includes the diagnostic categories of LSIL, HSIL and Carcinoma.

Table 12 CES Study EDP Sensitivity Results at 10% QC Review Rate

	Site 1	Site 2	Site 3	Site 4	Site 5	Site 6	All sites excl. Site 3[1]
Normal Review rate[2]	11.2%	11.8%	37.2%	9.4%	6.1%	19.3%	11.8%
All FNs[3]	32.0%	38.1%	56.5%	25.0%	37.6%	16.7%	34.5%
All FN-LSIL+[4]	66.7%	71.4%	100.0%	25.0%	42.9%	100.0%	52.4%

1 Site 3 is excluded from overall results due to incompatibility of staining procedure with the device.
2 Review Rate: Average percent identified as *QC Review* using the global 10% QC review rate.
3 All FNs: Includes the diagnostic categories of ASCUS, AGUS, LSIL, HSIL and Carcinoma.
4 All FN-LSIL+: Includes the diagnostic categories of LSIL, HSIL and Carcinoma.

Table 13 CES Study Results (CR review rate and sensitivity %) at 20% QC Review Rate

	Site 1	Site 2	Site 3	Site 4	Site 5	Site 6	All sites excl. Site 3[1]
Normal Review rate[2]	21.2%	28.0%	62.4%	19.5%	13.8%	29.4%	22.2%
All FNs[3]	48.3%	49.5%	76.3%	62.5%	47.2%	37.5%	48.1%
All FN-LSIL+[4]	80%	81.0%	N/A	33.3%	52.4%	50%	62.8%

1 Site 3 is excluded from overall results due to incompatibility of staining procedure with the device.
2 Review Rate: Average percent identified as *QC Review* using the global 10% QC review rate.
3 All FNs: Includes the diagnostic categories of ASCUS, AGUS, LSIL, HSIL and Carcinoma.
4 All FN-LSIL+: Includes the diagnostic categories of LSIL, HSIL and Carcinoma.

Table 14 CES Study IDP Sensitivity Results at 20% QC Review Rate

	Site 1	Site 2	Site 3	Site 4	Site 5	Site 6	All sites excl. Site 3[1]
Normal Review rate[2]	21.2%	28.0%	62.4%	19.5%	13.8%	29.4%	22.2%
All FNs[3]	53.2%	59.3%	75.9%	50.0%	48.4%	30.0%	49.7%
All FN-LSIL+[4]	100.0%	64.3%	100.0%	33.3%	43.2%	50.0%	49.1%

1 Site 3 is excluded from overall results due to incompatibility of staining procedure with the device.
2 Review Rate: Average percent identified as *QC Review* using the global 10% QC review rate.
3 All FNs: Includes the diagnostic categories of ASCUS, AGUS, LSIL, HSIL and Carcinoma.
4 All FN-LSIL+: Includes the diagnostic categories of LSIL, HSIL and Carcinoma.

Table 15 CES Study EDP Sensitivity Results at 20% QC Review Rate

	Site 1	Site 2	Site 3	Site 4	Site 5	Site 6	All sites excl. Site 3[1]
Normal Review rate[2]	21.2%	28.0%	62.4%	19.5%	13.8%	29.4%	22.2%
All FNs[3]	52.0%	59.5%	73.9%	50.0%	51.8%	16.7%	51.8%
All FN-LSIL+[4]	77.8%	85.7%	100.0%	25.0%	47.6%	100.0%	59.5%

1 Site 3 is excluded from overall results due to incompatibility of staining procedure with the device.
2 Review Rate: Average percent identified as *QC Review* using the global 10% QC review rate.
3 All FNs: Includes the diagnostic categories of ASCUS, AGUS, LSIL, HSIL and Carcinoma.
4 All FN-LSIL+: Includes the diagnostic categories of LSIL, HSIL and Carcinoma.

C.9 Historical Consistency Study (HC)

The Historical Consistency Study was designed to determine the effects on performance, if any, by age differences in processed samples. The study examined populations of cases originating from different time periods at the laboratory site. The study required 20 samples, each containing 64 WNL slides for a total of 1, 280 slides from each site. Kyto Diagnostics, L.P., and the University of Rochester both participated in this study.[31]

The results indicate no effects on the performance of the System (in terms of assignment of QC score) as a result of changes to slides caused by age or the consistency of staining over time.[32]

C.10 Study Sites and Investigators

Following are the names and addresses of each site participating in the Clinical Studies.

NeoPath, Inc.

1750-112th Avenue N.E, Suite B-101
Bellevue, WA 98004
Study Coordinator: Patricia A. Milbank, JD, RAC
VP, Regulatory Affairs/Quality Assurance

After February 24, 1995:

8271 154th Avenue
Redmond, WA 98052
Study Coordinator: Patricia A. Milbank, JD, RAC
VP, Regulatory Affairs/Quality Assurance

MetPath, Wood Dale (MetPath)/Corning Clinical Laboratories

1355 Mittel Boulevard
Wood Dale, IL 60191
Primary Investigator: D. Dax Taylor, MD,
Medical Director

Baptist Memorial Hospital (Baptist)

899 Madison Avenue, Room 280
Memphis, TN 38146
Primary Investigator: Shamim Moinuddin, MD,
Director of Cytopathology

Wishard Memorial Hospital (IU)

Department of Pathology
Indiana University
School of Medicine B029M
635 Barnhill Drive
Indianapolis, IN 46202-5120
Primary Investigator: Harvey Cramer, MD,
Director of Cytopathology

University of Rochester (UR)

601 Elmwood Avenue, Box 606
Rochester, NY 14642
Primary Investigator: David Wilbur, MD,
Director of Cytopathology

MDS, Toronto (MDS)

100 International Boulevard
Etobicoke, Ontario
Canada M9W 6J6
Primary Investigator: Terence J. Colgan, MD

Kyto Diagnostics, L.P. (Kyto)

216 Congers Road
New City, NY 10956
Primary Investigator: Ralph Richart, MD,
Medical Director

VIII. Conclusions Drawn from Studies

The results reported in the PMA show that the AutoPap® 300 QC System provides up to a 5-fold improvement over a 10% random selection method in the recovery of false negative slides.[33] This significantly better performance was demonstrated in a prospective study in actual intended-use mode at six clinical study sites: three academic institutions and three commercial clinical laboratories.

The significantly enhanced sensitivity of the device over a random selection method was shown to be true under all studied choices of threshold values (10%, 15% and 20%) for both overall false negatives (including ASCUS and AGUS) and at even higher efficiencies for those false negatives at severities of LSIL and above.

The consistency of these statistically significant improvements under a variety of scenarios overwhelmingly proves the effectiveness of the AutoPap® 300 QC System as a clinically significant device to reduce, in any laboratory, the frequency of false negative Pap smears.

The ability of the AutoPap® 300 QC System to identify undetected abnormal slides was supplemented by additional individual sensitivity studies on known abnormal slides, and by precision studies that demonstrate the overall consistency of the device.

Sensitivity was demonstrated for all classes of abnormalities across study sites; all the sensitivities were above the random selection

proportions generated by the various thresholds, both global and local. This consistent pattern of sensitivities above random selection ensured that the performance demonstrated in the intended-use prospective mode could be assured for any other combination of abnormal slides presented to the device; thus, significant improvement over random could be expected for any laboratory's prevalence rate of abnormals, type of abnormalities which occurred in the population served by the lab, and under any combination of accuracies available from local cytotechnologists in their initial screening abilities. The sensitivities of the device were demonstrated on both historical and current abnormal slides.

Imprecision was shown to have little apparent effect on the sensitivity of the AutoPap® 300 QC System to abnormal slides, as demonstrated by the virtually identical sensitivities achieved by the device upon repeated processing of the same set of slides. This consistency was demonstrated both in selected slide sets and in wide selections of local historical archived abnormal slides.

The Applicant of these clinical trials strongly believes that these evaluations were adequately designed, monitored, audited, conducted, and analyzed to show the effectiveness and, by extension, the safety of the AutoPap® 300 QC System.

The results demonstrate that this device reduces the risks associated with Pap smear screening for cervical cancer by improving the quality control process through detection of a significantly higher proportion of undetected abnormal slides than can be produced by random selection procedures. The use of this device can improve the accuracy and efficiency of the overall Pap smear screening Quality Control process, and significantly reduce false negatives from levels experienced with random selection Quality Control selection procedures.

IX. Panel Recommendations

On August 8, 1995, the *Hematology and Pathology Devices Panel* recommended that the FDA approve the Premarket Approval Application (PMA No. P950009) submitted by NeoPath, Inc., on February 24, 1995.

In addition, the panel recommended that the following limitations, which were suggested by the FDA Division of Clinical Laboratory Devices and agreed to by the Applicant, be included in the product insert:

1 The AutoPap® 300 QC System is to be used *only* on conventionally prepared Pap smear slides that have been previously classified as within normal limits (WNL) and satisfactory for interpretation by a cytology laboratory.

2 AutoPap® 300 QC System performance has not been established for use as a primary screener of Pap smears.

3 The AutoPap® 300 QC System is intended to detect evidence of squamous carcinoma and adenocarcinoma and their usual precursor conditions missed on prior manual microscopic examination of Pap smears. These abnormalities fall within the following diagnostic categories of The Bethesda System:

Epithelial Cell Abnormalities

Squamous Cell

Atypical squamous cells of undetermined significance (ASCUS)

Low-grade squamous intraepithelial lesions (LSIL)

High grade squamous intraepithelial lesions (HSIL)

Squamous cell carcinoma

Glandular Cell

Atypical glandular cells of undetermined significance (AGUS)

Endocervical adenocarcinoma

Endometrial adenocarcinoma

Extrauterine adenocarcinoma

4 The performance characteristics of the AutoPap® 300 QC System have not been established for the detection of the cervical abnormalities that fall within the following diagnostic categories of The Bethesda System:

- Benign cellular changes due to infection
- Reactive changes associated with inflammation, atrophy with inflammation, radiation, and intrauterine contraceptive device (IUD)
- Endometrial cells, cytologically benign, in a postmenopausal woman
- Adenocarcinoma, not otherwise specified (NOS) (specimen contains cellular evidence of adenocarcinoma but unable to further subclassify as to site of origin)
- Other malignant neoplasms

5 Use of the AutoPap® 300 QC System is intended to be performed only under the direct supervision of licensed and/or certified cytotechnologists, cytopathologists, or laboratory directors who have been trained and certified to use the AutoPap® 300 QC System by NeoPath, Inc., one of its subsidiaries, or an educational institution certified by NeoPath, Inc., to conduct training.

6 The AutoPap® 300 QC System is designed to be compatible with a wide range of staining procedures currently implemented in clinical laboratories. However, the device is *not* compatible with all staining methods currently in use. The compatibility of a laboratory's staining process will be assessed by NeoPath prior to clinical use of the device by the laboratory. If a modification to the staining procedure is indicated prior to use, NeoPath will provide the laboratory with suitable recommendations for consideration, testing and analysis. These procedures are intended to optimize the performance of the device while maintaining the integrity and current performance level of the human review process.

The AutoPap® 300 QC System is intended for use in processing only conventionally prepared cervical/vaginal Pap smear slides that meet the slide, coverslip, and staining characteristics provided in the Operator's Manual.

XII. CDRH Action on the Application

CDRH issued an approval order for applicant's PMA for AutoPap® 300 QC System to NeoPath, Inc. on September 29, 1995.

The applicant's manufacturing and control facilities were inspected September 5, 1995 through September 15, 1995 and the facilities were found to be in compliance with the Good Manufacturing Practice Regulations (GMPs).

XI. Approval Specifications

Directions for Use: See attached labeling.

Conditions of approval: CDRH approval of this PMA is subject to full compliance with the conditions described in the approval order (Attachment B).

Notes

[1] American Cancer Society. Cancer Facts and Figures–1993. 13–14.
[2] Kurman R.J. et. al. "Interim Guidelines for Management of Abnormal Cervical Cytology." JAMA 271 (June 15, 1994): 1866–1869.

[4] PMA, Vol. 14, Tab 14, Summary of Safety & Effectiveness, pp 003849–003850.
[5] PMA Amendments dated June 3, 1995; July 3, 1995; July 19, 1995; and September 8, 1995.
[6] PMA, Vol. 28, Tab 27, Papanicolaou Test for Cervical Cancer Detection, pp 006788–006794.
[7] PMA, Vol. 14, Tab 14, Summary of Safety & Effectiveness, pp 003849–003850.
[8] PMA, Vol. 13, pp 003319–003432.
[9] PMA, Vol. 13, pp 003432–003493.
[10] PMA, Vol. 14, Tab 14, Summary of Safety & Effectiveness, pp 003849–003850.
[11] PMA Amendments dated June 3, 1995; July 3, 1995; July 19, 1995; and September 8, 1995.
[12] PMA, Vol. 14, Tab 8, Sensitivity Studies, pp 003566–003567.
[13] PMA, Vol. 14, Tab 8, Sensitivity Studies, p 003608.
[14] PMA, Vol. 14, Tab 8, Sensitivity Studies, pp 003594–003595.
[15] PMA, Vol. 14, Tab 8, Sensitivity Studies, pp 003655–003657.
[16] PMA, Vol. 14, Tab 8, Sensitivity Studies, pp 003651, 003649.
[17] PMA, Vol. 14, Tab 8, Sensitivity Studies, pp 003657, 003655.
[18] PMA, Vol. 14, Tab 8, Sensitivity Studies, pp 003616, 003655.
[19] PMA Amendment dated July 19, 1995.
[20] PMA Amendment dated July 19, 1995.

NeoPath, Inc.
AutoPap® 300 QC System

Product Insert

Date: September 29, 1995

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1 Intended Use

The AutoPap® 300 QC System is an automated cervical cytology rescreening device intended for use in the quality control and rescreening of previously screened Papanicolaou (Pap) smear slides. The AutoPap® 300 QC System is to be used *only* on conventionally prepared Pap smear slides that have been previously classified as within normal limits (WNL) and satisfactory for interpretation by a screening cytologist.

The AutoPap® 300 QC System is not intended to replace the current laboratory slide review processes referred to as "high-risk rescreen."

2 Summary and Explanation of the System

The AutoPap® 300 QC System is an automated cytology rescreening device that uses a high-speed video microscope, image interpretation software, and specially designed field-of-view computers to image, analyze, and classify cells within the complex images on a Pap smear slide.

The AutoPap® 300 QC System is intended to detect evidence of squamous carcinoma and adenocarcinoma and their usual precursor conditions missed on prior manual microscopic examination of Pap smear slides. These abnormalities fall within the following diagnostic categories of The Bethesda System:

Epithelial Cell Abnormalities

Squamous Cell

Atypical squamous cells of undetermined significance (ASCUS)

Low-grade squamous intraepithelial lesions (LSIL)

High-grade squamous intraepithelial lesions (HSIL)

Squamous cell carcinoma

Glandular Cell

Atypical glandular cells of undetermined significance (AGUS)

Endocervical adenocarcinoma

Endometrial adenocarcinoma

Extrauterine adenocarcinoma

Pap smear slides screened as WNL and adequate for analysis by a screening cytotechnologist are to be rescreened by the AutoPap® 300 QC System. Based on cytologic evidence, the device then identifies, for manual quality control (QC) review, slides with the highest probability of being a false negative to create an enriched sample. The result is that there is a higher prevalence of false negative slides in the sample selected for manual QC review.

The System classifies each slide into one of three categories:

QC Review
Further human review recommended; specimen is potentially abnormal;

No Review
No evidence to recommend further human review; or,

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Review

Squamous component not detected or slide not successfully processed. The slide may be able to be reprocessed based on the information provided in the slide report and the instructions provided in the *Operator's Manual.* If a slide cannot be successfully reprocessed, it is recommended that the laboratory conduct its usual procedure for routine QC selection.

In some cases, if a slide cannot be successfully reprocessed, manual microscopic review may be recommended because the reason for failure to scan may indicate a likelihood that the specimen is potentially unsatisfactory. The *Operator's Manual* provides guidelines for identifying and handling such slides.

The laboratory also should select for manual microscopic review the Pap smear slides from patients or groups of patients that have been identified as having a high probability of developing cervical cancer, based on available patient information.

3 Limitations

AutoPap® 300 QC System performance has *not* been established for use as a primary screener of Pap smears.

Clinical data demonstrated that use of the AutoPap® 300 QC System will improve the recovery of false negative slides in the laboratory over a random selection method. However, this device does not recover all false negative slides: false negative readings should still be expected to occur with the use of this device.

The AutoPap® 300 QC System is not intended or recommended for use as a confirmatory screener for slides that have been previously classified as abnormal or unsatisfactory for interpretation.

The performance characteristics of the AutoPap® 300 QC System have not been established for the detection of the cervical abnormalities that fall within the following diagnostic categories of The Bethesda System:

- Benign cellular changes due to infection
- Reactive changes associated with inflammation, atrophy with inflammation, radiation, and intrauterine contraceptive device (IUD)
- Endometrial cells, cytologically benign, in a postmenopausal woman
- Adenocarcinoma, not otherwise specified (NOS) (specimen contains cellular evidence of adenocarcinoma but unable to further subclassify as to site of origin)
- Other Malignant Neoplasms

Use of the AutoPap® 300 QC System is intended to be performed under only the direct supervision of licensed and/or certified cytotechnologists, cytopathologists, or laboratory directors who have been trained and certified to use the AutoPap® 300 QC System by NeoPath, Inc., one of its subsidiaries, or an educational institution certified by NeoPath, Inc., to conduct training.

The AutoPap® 300 QC System is designed to be compatible with a wide range of staining procedures currently implemented in clinical laboratories. However, the device is *not* compatible with all staining methods currently in use. The compatibility of a laboratory's staining process will be assessed by NeoPath prior to clinical use of the device by the laboratory. NeoPath may recommend alternate staining procedures intended to optimize the performance of the device while maintaining the integrity and current performance level of the human review process.

The AutoPap® 300 QC System is intended for use in processing only conventionally prepared cervical/vaginal Pap smear slides that meet the slide, coverslip, and staining characteristics provided in the *Operator's Manual.*

This device is intended for use only with glass microscope slides and glass coverslips.

4 Warnings

Moving Parts Hazard when Loading/Unloading Trays

Remove all potentially obstructive jewelry and clothing before loading or unloading trays. After opening a hopper door, be sure all moving parts in the hopper have stopped before inserting or removing a tray. If trays are inserted before all moving parts have stopped, injuries may occur or the device may jam.

Shock Potential when Cleaning the Monitor

Failure to remove power to the monitor before performing the procedure could result in an electric shock. See the *Operator's Manual.*

Shock Potential when Power Applied Improperly

The symbol next to the power connector indicates potential shock hazard. Ensure that the system is connected to a power receptacle that provides voltage and current within the specified rating for the system. Use of an incompatible power receptacle may produce electrical shock and fire hazards.

Shock Potential when Improperly Grounded

Never use a two-prong plug adapter to connect primary power to the system. Use of a two-prong adapter disconnects the utility ground, creating a potential shock hazard. Always connect the system power cord directly to an appropriate receptacle with a functional ground.

Shock Potential when Cleaning with Power Applied

Always turn off the power switch and unplug the power cord before cleaning the outer surfaces or internal components of the device.

Shock Potential from Spilled Liquids

Do not place containers with liquids on the device or the workstation cart. Do not spill liquids on the system; fluid seepage into internal components creates a potential shock hazard. Shut down the device, disconnect from the power source, and wipe up all spills immediately. Do not operate the system if internal components have been exposed to fluid.

5 Precautions

Compliance with Standards

Prior to using the device, a laboratory must ensure that the use of the AutoPap® 300 QC System as a quality control method complies with all applicable federal, state, and local requirements for that laboratory. NeoPath will provide available information and assistance in this regard upon request.

Slide and Coverslip Requirements

This device is intended for use with only glass microscope slides and glass coverslips.

This device cannot be recommended for use with slides and coverslips that do not comply with the specifications provided in the *Operator's Manual*, particularly slides with plastic coverslips, broken slides, dirty or marked slides, and non-standard slide or coverslip sizes.

Backup Procedures

When performing the backup procedures, use a new computer tape each day. The system will not overwrite a previously used computer tape.

Shutdown Procedures

Except in an emergency situation, such as those described in the *Warnings* section, shutting down the AutoPap® 300 QC System should be performed only with prior authorization of a company representative to avoid loss of data. If no emergency situation exists, contact NeoPath, Inc., or its designated representative before attempting to shut down the device.

Power Down Procedures

It is important to shut down the system components in the proper order. See the *Operator's Manual*.

Restart Procedures

The AutoPap® 300 QC Workstation must always be turned on and booted *before* the AutoPap® 300 QC System is turned on. It is important to apply power to the system components in the proper order. See the *Operator's Manual*.

Installation and Service

The device should be installed only by company authorized personnel. Only technically qualified personnel, trained by NeoPath, Inc., should perform troubleshooting and service procedures on internal components.

Replacement Fuses

Use replacement fuses with the required current rating and specification. Using improper fuses or short-circuiting the fuse holders may cause a fire or damage the device.

6 Reports of Clinical Studies

Several multi-center, well-controlled clinical studies were conducted to evaluate the performance of the device. An intended use study confirmed the accuracy of the AutoPap® 300 QC System in a masked, prospective design. Several sensitivity and precision studies were conducted to confirm the performance characteristics and reliability of the device.

6.1 Accuracy Study: The Clinical Evaluation Study

The Clinical Evaluation Study was designed to compare the effectiveness of a random selection quality control practice in a cytology laboratory to the effectiveness of the AutoPap® 300 QC System using a quality control application. The AutoPap® 300 QC System was operated, as nearly as possible, in a manner similar to that recommended for routine laboratory use.

The objective of the study was to test the hypothesis that the device is capable of providing a higher proportion of false negative slides for quality control review than can be achieved by a random selection method. This hypothesis was evaluated over a range of quality control review rates.

A 100% manual rescreen of all processed slides was performed in this study to identify, as nearly as possible, the total population of false negative slides available for review. This population of false negative slides was then used as the target population to measure the efficacy of the device in identifying these false negative slides at a 10% QC review rate.

The study design ensured that the site personnel were effectively masked and enhanced the probability of detecting the false negative slides present within the entire study population. The total number of slides used in the analysis was 14,914.

Each false negative slide recovered during the study was reviewed by an Internal Discrepancy Panel of study site personnel as well as an External Discrepancy Panel of independent pathologists. The results of the External Discrepancy Panel review are used to demonstrate the efficacy of the device.

These results demonstrate that the AutoPap® 300 QC System identifies a subset of manual screen negative Pap smear slides that have been enriched through computer selection for false negative slides. A manual screening of this enriched subset (10% of the total manual screen negative slides) will identify up to 50% of false negatives when compared to a 100% manual rescreen. This compares to the expected identification of only 10% of false negatives by a completely random selection review.

Table 1 Clinical Evaluation Study
Sensitivity to False Negative Slides by Diagnostic Category and Overall
10% QC Review Rate, % Sensitivity, (N)

	Site 1	Site 2	Site 3	Site 4	Site 5	Site 6	All sites excluding Site 3[1]
Review Rate[2]	11.2%	11.8%	37.2%	9.4%	6.1%	19.3%	11.8%
FN-ASCUS	22.5%	36.7%	47.4%	33.3%	35.7%	0.0%	29.7% (41/138)
FN-AGUS	100.0%	20.0%	100.0%	0.0%	37.5%	50.0%	29.4% (5/17)
FN-LSIL	57.1%	83.3%	100.0%	0.0%	42.9%	100.0%	51.6% (16/31)
FN-HSIL	100.0%	NA	NA	100.0%	42.9%	NA	60.0% (6/10)
FN-Cancer	NA	0.0%	NA	NA	NA	NA	0.0% (0/1)
All FN[3]	32.0%	38.1%	56.5%	25.0%	37.6%	16.7%	34.5% (68/197)
All FN-LSIL+[4]	66.7%	71.4%	100.0%	25.0%	42.9%	100.0%	52.4% (22/42)

1 Site 3 is excluded from overall results due to incompatibility of staining procedure with the device.

2 Review Rate: Average percent identified as *QC Review* using the global 10% QC review rate.

3 All FNs: Includes the diagnostic categories of ASCUS, AGUS, LSIL, HSIL and Carcinoma.

4 All FN-LSIL+: Includes the diagnostic categories of LSIL, HSIL and Carcinoma.

Analysis of the overall performance of the device in detecting the presence or absence of an endocervical component shows the following:

- 85% of normal slides with endocervical component are correctly classified. 15% of the normal slides with endocervical component are reported as "endocervical component not detected." However, this result does not affect the computation of the QC score.
- 73% of normal slides without endocervical component are correctly classified.

6.2 *Sensitivity Studies*

Two large, multi-center sensitivity studies were performed using abnormal slides. Each selected abnormal slide required a normal matched control slide.

The Current Archive Sensitivity Study used recent abnormal slides processed by each laboratory. The diagnostic categories selected included ASCUS, AGUS, LSIL, HSIL, cancer (squamous, glandular, and extrauterine) and detected false negative slides. The total number of slides used in the analysis, including matched controls, was 2,584.

The Historical Archive Sensitivity Study used abnormal slides retrieved from the archived records of each trial site. The diagnostic categories selected included AGUS, LSIL, HSIL, cancer (squamous, glandular, and extrauterine) and detected false negative slides. The total number of slides used in the analysis, including matched controls, was 3,589 (see Table 2).

Table 2 Sensitivity to Abnormal Slides by Diagnostic Category
Historical Sensitivity Study
10% QC Review Rate, % Sensitivity, (N)

	Site 1	Site 2	Site 3	Site 4	Site 5	Site 6	All Sites (excluding Site 3[2])
AGUS	45.0% (80)	33.3% (30)	60.0% (5)	45.9% (37)	N/A	34.4% (96)	39.5% (243)
LSIL	67.4% (89)	62.2% (90)	68.3% (63)	68.7% (67)	46.2% (80)	60.5% (86)	60.9% (412)
HSIL	84.7% (85)	79.0% (81)	90.4% (73)	87.7% (57)	70.3% (74)	88.6% (88)	82.1% (385)
CANCER	100.0% (21)	86.5% (52)	66.7% (3)	61.5% (26)	50.0% (2)	71.1% (38)	79.1% (139)
Review Rate[1]	16.5%	18.5%	34.2%	13.3%	7.6%	10.4%	11.9%

1 Review Rate: Average percent identified as *QC Review* at each laboratory using the global 10% QC review rate.
2 Site 3 is excluded from overall results due to incompatibility of staining procedure with the device.

The data derived from processing these abnormal slides demonstrate that the AutoPap® 300 QC System has improved sensitivity to all tested categories of abnormal slides (see Table 3).

Table 3 Sensitivity to Abnormal Slides by Diagnostic Category
Current Archive Study (CAS) and Historical Sensitivity Study (HSS)
10% QC Review Rate, % Sensitivity, (N)

	ASCUS	AGUS	LSIL	HSIL	CANCER
CAS	36.1% (205)	27.3% (22)	60.0% (410)	80.2% (202)	62.5% (8)
HSS	N/A	39.5% (243)	60.9% (412)	82.1% (385)	79.1% (139)

An analysis was conducted of the subset of cancer slides retrieved from the archived records. This subset represented the larger sample size from the two sensitivity studies. The sensitivity rates, by subclassification category, are reported in Table 4. (These subclassifications are derived from the procedures used across all the participating laboratories and may not coincide with individual laboratory practice.)

These results show the device has a significant sensitivity to cancer slides.

Table 4 Sensitivity to Subset of Cancer Slides
10% QC Review Rate, % Sensitivity, (N)

Squamous CA[1]	AdenoCA NOS[2]	Malignant NOS	Endocervical AdenoCA	Endometrial AdenoCA	AIS[3]	All Cancer Slides
91.3%	52.6%	40.0%	100.0%	66.7%	58.8%	77.7%
(80)	(19)	(5)	(3)	(15)	(17)	(139)

1 CA: Carcinoma

2 NOS: Not otherwise specified (specimen contains cellular evidence of adenocarcinoma but unable to further subclassify as to site of origin)

3 AIS: Adenocarcinoma in situ

A second subset analysis was conducted for the HSIL and cancer slides identified by the clinical trial sites as having a biopsy-confirmed diagnosis. The slides were selected from both the Historical Sensitivity Study and the Current Archive Sensitivity Study.

These results indicate the device has a significant sensitivity to biopsy-confirmed HSIL and cancer slides (see Table 5).

Table 5 Sensitivity to Subset of Biopsy-Confirmed HSIL and Cancer Slides
10% QC Review Rate

	No. of Biopsies	No. of Biopsies Confirmed	Confirmed Biopsies Called "QC Review"	% Sensitivity
HSIL	60	51	43	84.3%
Cancer	35	33	22	66.7%
Total	95	84	65	77.4%

6.3 *Precision Studies*

Two studies were conducted to assess precision, or repeatability, of the device. The first study was the Multi-Run Standardized Sample Set Study which used a set of 32 well-characterized slides that were processed up to 30 times on each of three separate devices. Of the 32 slides, 25 demonstrated 100% repeatability (see Table 6). The average percent agreement on all slides was 99.6% overall. These results confirm that the repeatability of the device in calling a slide *QC Review* or *No Review* is consistent from device to device (inter-device repeatability) and within each tested device (intra-device repeatability).

Table 6 Summary Results of Precision Study (Multi-Run of Standardized Sample Set)
% Repeatability of QC Review/No Review Outcome for Each Slide

Barcode	QC Review No Review	Site 0	Site 1	Site 4	Overall	Diagnosis
940006439	No Review	100%	100%	100%	100%	Normal
940006443	No Review	100%	100%	100%	100%	Normal
940006464	No Review	100%	100%	100%	100%	Normal
940006467	No Review	100%	100%	100%	100%	Normal
940006472	No Review	100%	100%	100%	100%	Normal
940006473	No Review	100%	100%	100%	100%	Normal
940006476	No Review	100%	100%	96%	99%	Normal
940006487	No Review	97%	93%	100%	96%	Normal
940006489	No Review	100%	100%	100%	100%	Normal
940006492	No Review	100%	100%	100%	100%	Normal
940006493	No Review	100%	100%	100%	100%	Normal
940006497	No Review	NA	100%	96%	98%	Normal
940007379	QC Review	100%	100%	96%	99%	ASCUS
940007381	QC Review	97%	100%	100%	99%	ASCUS
940007409	QC Review	100%	100%	96%	99%	ASCUS
940007410	QC Review	97%	100%	96%	98%	ASCUS
940007416	QC Review	100%	100%	100%	100%	ASCUS
921011542	QC Review	100%	100%	NA	100%	AGUS
940006420	QC Review	100%	100%	100%	100%	LSIL
940006425	QC Review	100%	100%	100%	100%	LSIL
940006428	QC Review	100%	100%	100%	100%	LSIL
940006430	QC Review	100%	100%	100%	100%	LSIL
940006436	QC Review	100%	100%	100%	100%	LSIL
940006390	QC Review	100%	100%	100%	100%	HSIL
940006393	QC Review	NA	100%	100%	100%	HSIL
940006397	QC Review	100%	100%	100%	100%	HSIL
940006398	QC Review	100%	NA	100%	100%	HSIL
940007261	QC Review	100%	NA	100%	100%	HSIL
921011561	QC Review	100%	100%	100%	100%	HSIL/CIS[1]
921011562	QC Review	100%	100%	100%	100%	HSIL/CIS
921011565	QC Review	100%	100%	100%	100%	HSIL/CIS
921011574	QC Review	NA	100%	NA	100%	SquamCarc

1 CIS = Carcinoma in situ

The second precision study required three processing runs of the abnormal slides selected by each laboratory for use in the Historical Sensitivity Study. The total number of slides used in the analysis was 10,674. The results demonstrate that the device produces substantially equivalent sensitivity estimates when repeatedly processing large sets of abnormal and matched control slides. The data presented illustrates a high degree of between-run agreement overall (see Table 7).

Table 7 Combined Results of Precision Study Multi-Run of Historical Sensitivity Study Slide Set
10% QC Review Rate, % Sensitivity

		AGUS	LSIL	HSIL	CANCER	Review Rate[1]
Site 1	Run 1	45.0%	67.4%	84.7%	100.0%	16.5%
	Run 2	48.1%	72.0%	86.2%	100.0%	14.8%
	Run 3	43.6%	72.7%	87.1%	100.0%	16.3%
Site 2	Run 1	33.3%	62.2%	79.0%	86.5%	13.5%
	Run 2	36.7%	54.4%	80.5%	85.0%	12.3%
	Run 3	33.3%	57.6%	84.0%	87.8%	15.6%
Site 3[2]	Run 1	60.0%	68.3%	90.4%	66.7%	34.2%
	Run 2	50.0%	75.7%	95.5%	75.0%	32.2%
	Run 3	40.0%	68.5%	92.2%	75.0%	27.5%
Site 4	Run 1	45.9%	68.7%	87.7%	61.5%	13.3%
	Run 2	52.8%	71.2%	83.6%	53.1%	11.0%
	Run 3	41.9%	66.7%	91.2%	57.1%	13.8%
Site 5	Run 1	N/A	46.2%	70.3%	50.0%	7.6%
	Run 2	N/A	37.2%	74.3%	50.0%	6.7%
	Run 3	N/A	42.9%	68.7%	100.0%	7.1%
Site 6	Run 1	34.4%	60.5%	88.6%	71.1%	10.4%
	Run 2	32.6%	62.9%	84.2%	72.7%	10.8%
	Run 3	30.7%	54.9%	84.8%	69.0%	10.5%

1 Review Rate: Average percent identified as *QC Review* at each laboratory using the global 10% QC review rate.

2 Site 3 is excluded from overall results due to incompatibility of staining procedure with the device.

6.4 *Historical Consistency Study: Effects Caused by Age of Slides*

The Historical Consistency Study was conducted to confirm the effects on the device, if any, caused by changes in staining and slide age. The results indicate no effects on the performance of the device (in terms of assignment of QC score) as a result of changes to slides caused by age or the consistency of staining over time.

7 Conclusions Drawn from Studies

The results from the Clinical Evaluation Study, a masked, prospective study using the device in an intended-use mode, show that the AutoPap® 300 QC System identifies a subset of manual screen negative Pap smear slides that have been enriched through computer selection for false negative slides. A manual screening of this enriched subset (10% of the total manual screen negative slides) will identify up to 50% of false negatives when compared to a 100% manual rescreen. This compares to the expected identification of only 10% of false negatives by a completely random 10% manual review.

In addition, the data results show that the device has a significant sensitivity to cancer slides and to biopsy-confirmed HSIL and cancer slides.

The sensitivity of the device over a random selection method was shown to be true under all studied review rates (10%, 15% and 20%) for all claimed diagnostic categories of false negatives (including ASCUS and AGUS) and at even higher efficiencies for those false negatives at severities of LSIL and above.

Acceptable sensitivities were demonstrated for all categories of abnormality across study sites; all the sensitivities were above the random selection proportions generated by the various thresholds selected for study. This consistent pattern of sensitivities above random selection ensured that the performance demonstrated in the intended-use prospective mode could be assured for any other combination of abnormal slides presented to the device; thus, significant improvement over random could be expected for any laboratory's prevalence rate of abnormals and type of abnormalities, and under any combination of cytotechnologist sensitivities at initial screening. The sensitivities of the device were further demonstrated on both current and archived abnormal slides.

The AutoPap® 300 QC System demonstrated virtually identical sensitivities upon repeated processing of standard sets of slides. This consistency was demonstrated both in selected slide sets and in wide selections of archived abnormal slides.

The results demonstrate that this device detected a higher proportion of undetected abnormal slides than can be produced by random selection procedures.

8 Materials

8.1 Materials Provided

The AutoPap® 300 QC System consists of the following components:

- AutoPap® 300 QC Device
- Nitrogen tank
- Slide trays (40)
- Workstation:
  - Computer (CPU)
  - Monitor, Keyboard, Mouse, Mouse Pad
  - Modem
  - Printer
  - Tape Drive
  - Ethernet Transceiver Unit
  - Cart
- Electronic Cables: Ethernet, Printer to Ethernet, AutoPap to CPU, Monitor to CPU, Tape drive to CPU, Modem to CPU, Keyboard to CPU
- Power Strip (6-outlet)
- Power Cords: Device, CPU, Monitor, Printer, Tape Drive, Modem

Additional items supplied:

- Printer Paper (starter package)
- Head Cleaning Tape
- Slide Barcode Labels
- Backup Tapes
- Line Protector and/or Power Supply (optional)
- SCSI Bus Terminator
- Air Filters

8.2 *Materials Required But Not Provided*

- Dedicated 20 amp power line
- Dedicated 15 amp power line
- Telephone line
- Dustproof bins to store empty slide trays
- 70% Isopropyl Alcohol
- Cotton swabs or soft bristle brush
- Lint-free cloth
- Glass cleaning solution (non-alcohol based)

8.3 *Storage*

Do not expose the system to direct sunlight or temperature extremes (that is, air flow from heating or cooling systems).

9 *Technical Service and Product Information*

For technical service and assistance related to use of the AutoPap® 300 QC System, contact NeoPath:

Telephone: 1-800-NEOPATH (outside Washington State) (1-800-636-7284)

1-206-869-7284 (inside Washington State)

Fax: 1-206-869-5325