

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name:	Liquid-based Cervical Cytology Slide Preparation Device
Device Trade Name:	MonoPrep Pap Test (MPPT)
Applicant's Name and Address:	MonoGen, Inc. 2461 East Oakton Street Arlington Heights, IL 60005
Date of Panel Recommendation:	None
Premarket Approval Application Number:	P040052
Date of Notice of Approval to Applicant:	March 3, 2006

II. INDICATIONS FOR USE

Intended Use

The MonoPrep Pap Test (hereinafter called MPPT) is intended for use in collecting and preparing cervical-vaginal cytology specimens for Pap stained-based screening for cervical cancer, its precursor lesions and other cytologic categories and conditions defined by The 2001 Bethesda System: terminology for reporting results of cervical cytology⁽¹⁾. The MonoPrep Pap Test produces slides that are intended to replace conventionally prepared Pap smear slides.

III. CONTRAINDICATIONS

There are no known contraindications for use.

IV. WARNINGS AND PRECAUTIONS

Warnings and precautions for use of the device are stated in the MonoGen MonoPrep Pap Test labeling (Attachment 1).

DEVICE DESCRIPTION

The MonoGen MonoPrep Pap Test (MPPT) system is a device which converts a liquid suspension of cervical cells into a thin-layer of cells deposited on a glass microscope slide for Papanicolaou staining and analysis. The components of the MPPT system are described below.

Cervical Specimen Collection Device

An FDA-approved endocervical cytobrush and a plastic cytospatula are provided for use with the MPPT. Break-away-tip collection devices may not be used with the MPPT.

MonoPrep Pap Test Specimen Collection Vial with Integrated Cap/Stirrer containing MPPT Specimen Transport Solution

The MPPT collection vial has a detachable stirrer with vanes attached to a hollow tube which ensures specimen mixing and dispersal of mucus and loose specimen clumps as well as aspiration of the sample. The MPPT Specimen Transport Solution is a buffered alcohol preservation solution which is tinted for identification purposes.

MonoPrep Pap Test Filters GYN

The MPPT Filter GYN is a single-use, disposable item designed for gynecological specimens. The filter consists of an acrylic housing and frit-backed filter membrane. The frit supports the filter and facilitates transfer of the sample from the filter to the slide. Fifty MPPT GYN Filters are packaged in a tube which loads directly into the MPPT Processor.

MonoPrep Pap Test Processor

The MonoPrep Processor is an automated platform for cytology specimen processing consisting of the following stations: loading station; uncapping station; mixing station; filter dispensing station; aspiration station; fixative station; slide printing station; vial resealing station; and slide cassette elevating and holding station. Specimen vials can be loaded directly onto the conveyor belt or in autoloader trays. The processor can hold up to six trays each holding 54 specimen vials and one cleaning vial allowing 324 specimens to be processed unattended in an eight-hour run.

The MonoPrep Processor's automated specimen processing steps include: vial uncapping; spinning the vial stirrer; dispensing the appropriate filter onto the stirrer manifold; providing aspiration vacuum for the filter; lowering the filter onto the MonoPrep slide; dispensing MonoPrep Fixative Solution onto the prepared slide; replacing the prepared slide and vial back into their respective cassette and tray; and registering the slide barcode with the data management system.

There are two types of processing parameters that can be used for GYN slides, GYN-Normal and GYN-Alternative. These parameters are entered into the laboratory's data management system which interfaces with the MonoPrep Processor. The decision as to which processing parameters to set for a specimen is selected at vial accessioning and the parameters differ only in the method used to determine the time period for aspirating the specimen through the MPPT filter. Both methods use the same controlled parameters for stir speed, stir time, filter type, number of slides prepared, and number of fixative drops dispensed.

The GYN-Normal (turbidity-based aspiration control) was designed for processing a

range of normal specimens. The turbidity measurement estimates the concentration of cells in the specimen and calculates the time period needed to aspirate a sufficient amount of specimen through the filter membrane in order to collect the target number of cells on the filter.

The GYN-Alternative (flow-based aspiration control) is an alternate method for processing unusual specimens that are excessively bloody, have large numbers of inflammatory cells, or that require reprocessing as a result of a previously produced unsatisfactory (UNSAT) slide. In flow-based aspiration, the flow rate across the membrane decreases as the number of cells adhering to the membrane increase and block the filter pores. The aspiration of cells is ended when the reduction in flow rate indicates that the target number of cells has been collected on the filter membrane.

MonoGen Data Management System

The Savant Data Management System (DMS) is a Laboratory Information System (LIS) that provides basic LIS data storage and transmission functions for the MonoPrep Processor. The DMS/LIS provides specimen vial accessioning with the user entering the vial number by keyboard or standard barcode scanner and then selecting the processing parameter set for the specimen.

VI. ALTERNATIVE PRACTICES OR PROCEDURES

The conventional Papanicolaou smear (Pap smear) is the original well-established method for screening women for cervical neoplasia or its precursor lesions. It consists of scraping cells from the cervix and manually spreading them onto a glass slide for examination by a cytopathologist. Liquid-based cervical cell collection preparations are an alternative to the Pap smear method. With the liquid-based methods, the cells are scrapped from the cervix, rinsed into the collection fluid vial, and deposited in a thin-layer onto a glass slide for examination by a cytologist. There are two previously approved liquid-based slide preparation methods.

VII. MARKETING HISTORY

The MonoPrep Pap Test system has not been marketed in the United States or any foreign country.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Specimen preparation errors may result in false negative or false positive diagnoses. A false negative diagnosis may result when there are no abnormal cells on the slide when disease is actually present. False negative diagnoses result in delayed diagnosis and treatment for the patient. A false positive diagnosis may result when normal cells appear abnormal due to faulty slide preparation and no disease is present. As a result the patient may have an unnecessary colposcopy exam (a non-invasive procedure) or may be referred for biopsy (an invasive procedure).

IX. SUMMARY OF PRECLINICAL STUDIES

A. Preclinical Studies

The pre-clinical studies for the MonoGen MonoPrep Pap Test (MPPT) system were designed to assess the (1) MPPT Cell Morphology and Presentation, (2) MPPT Component Selection and Robustness, and (3) MPPT Processing Steps.

1. The Cell Morphology and Presentation series included the following studies: Target Cellularity; Morphological Stability of Specimens, Long Term Preservation; and Specimen Stability Under Varying Conditions.

In the Target Cellularity study, epithelial cell nuclear morphology, endocervical component morphology, cell distribution, cell density, thinness of cell layer, presentation of diagnostic material, and abundance of cellular material were evaluated by experienced cytotechnologists and cytopathologists. The results of the study indicated that the slides conformed to the design requirements when prepared in the specified manner. In a random sample of slides from the pivotal clinical study, the number of squamous epithelial cells on a slide ranged from 27,000 to 143,000, in 90% of the slides. The average number of squamous epithelial cells was 60,000 with 95%CI: 42,000~78,000.

The Morphological Stability of Specimens: Long Term Preservation study evaluated 34 residual specimens from the clinical trial which were stored at ambient room temperature (15-30°C) for a period of time ranging from 9 to 14.9 months. A second slide (MP2) was prepared and compared with MP1 from the clinical trial. A cytopathologist that participated in the clinical trial read both slide pairs to evaluate them for diagnostic concordance and any other observed differences between the two slide pairs that could affect the diagnosis. The results indicate that for 34 abnormal slide pairs, 26 (76%) received the same diagnosis. In the remaining 8 cases, the diagnoses for the pair differed by one category. In three cases the MP1 diagnosis was higher and in 5 cases, MP2 was higher. This study indicates that for specimens stored at room temperature (15-30°C) for up to a year, the preservation of diagnostic morphology in abnormal cervical cytology specimens mostly permits reproducible diagnosis.

The Specimen Stability Under Varying Conditions study was designed to demonstrate that MPPT vials with specimens exposed to boundary (2°C, 30°C) and stress (-20°C, 55°C) conditions does not affect the ability of the GYN-Normal aspiration system to provide satisfactory cell depositions. A LSIL specimen pool was used for the incubation at these testing temperatures and times: 2-8°C overnight; 30°C overnight; -20°C eight hours; and 55°C six hours. Five replicate slides were made from each vial and were reviewed in a masked fashion. It was determined that after exposure to these temperatures there was no material effect on diagnostic morphology or specimen diagnosis.

2. The Component Selection and Robustness series includes the following studies: Filter Quality and Defect Analysis; Vial Label, Slide Mask, and Barcode

Robustness; Stability of Fixative and Specimen Transport Solution; and Specimen Transport Solution Anti-Microbial Effectiveness.

The Filter Quality and Defect Analysis study tested the ability of damaged MPPT filters to produce satisfactory slides and to determine the defects that should be detected in the manufacturing process to keep known deficient filters from commercial distribution. Filters were deliberately damaged before being used to process slides from pooled specimens. The study results showed that all the slides produced were rated satisfactory according to the Bethesda System 2001 criteria, but some of the slides had incomplete cell deposition with low cell densities. The conclusion is that slides with defects such as torn or split membranes, membrane folds or creases, and those with portions of the membrane missing should be rejected, but imperfections such as bumps in the frit, small pin holes, or divots in the material had a negligible impact on slide quality.

The Vial Label, Slide Mask, and Barcode Robustness study tested the labels on the vial and slide to see if they were sufficiently durable to withstand prolonged exposure to the solutions to which they are exposed during processing on the MPPT system. The vial label contains two barcodes, the lot number and expiration date, while the slide contains a barcode and mask. After exposure to MPPT Specimen Transport Solution and cleaner solution, all were successfully displayed and read on the MPPT Processor.

The Stability of Fixative and Specimen Transport Solution study tested the compositional stability of the Specimen Transport Solution, fixative, slides, vials, bags and the seal integrity of the vial and bag configuration under expected and extreme shipping and storage conditions using standard compositional assays. One lot of MPPT-STS vials was tested as capped-sealed and foil-sealed. Testing temperatures were ambient room temperature (ART) (15-30°C); lower limit and cold stress (-20°C, 2-8°C); and upper limit and heat stress (37°C, 55°C). The results of this testing indicated that the alcohol content, ratio, and pH of the MPPT-Specimen Transport Solution remain within specifications for all tested conditions and time-points.

The Specimen Transport Solution turbidity measurements at 55°C for 24 hours showed a 28-61% decrease below the baseline. Holding the Specimen Transport Solution at 55°C for 6 hours produced only a slight decrease in turbidity resulting in a maximum stability claim of 6 hours at 55°C. Thus the stability claims are as follows: Specimen Transport Solution collection vials with and without specimen is 12 months at 15-30°C; 3 weeks at 2-37°C; and 6 hours at -20 to 55°C.

In the Specimen Transport Solution Anti-Microbial Effectiveness study, the STS was tested by an accredited laboratory for anti-microbial effectiveness per the United States Pharmacopoeia 26 methodology. The five microorganisms tested were *S. aureus*; *E. coli*; *P. aeruginosa*; *C. albicans*; and *A. niger*. No testing or claims were made for *Mycobacterium tuberculosis*. The MPPT-STS met the USP requirements for all tested organisms.

3. The MPPT Processing Steps series includes the following studies: Filter to

Slide Transfer Efficiency; Equivalence of Cell Deposition with Two Different Types of Filters; Control of Cellular Cross Contamination; and Potential Interference by Extraneous Materials.

Filter to Slide Transfer Efficiency

The objective of the filter transfer efficiency study was to validate the number of squamous epithelial cells transferred from a filter to a slide; the efficiency of cell transfer; and the transfer of abnormal cells using filters made with pressed frits and compared with the performance of filters made with the original machined frits. Three pools of LSIL specimens using time-based aspiration were used with the two filter types to make a total of 6 slides. Squamous and abnormal cell numbers on the slides were determined by counting the cells in 10 reticule fields-of-view across the diameter of each cell deposition as recommended by the Bethesda System 2001 method. The filters were removed so that the number of abnormal cells could be counted and the number of squamous epithelial cells estimated. Only the abnormal cells on the filter were directly counted by reviewing the entire filter area using a 20X objective. The results indicate that for these 6 slides, the transfer of cells from the filter to slide was 99% for the cut frits and 97.0% for the pressed frits. Abnormal cells were not preferentially retained on either filter type. Though only a small number of slides were tested, the performance of the two different types of filters appears to be similar.

Equivalence of Cell Deposition with Two Different Types of Filters

The objective of this study was to use a larger sample size to further confirm the results from the previous study that there is no difference between the two different manufactured types of filters when measuring the transferred cellular material and the numbers of abnormal cells retained on the filters. This study used a sample size of 10 vials of LSIL pools. Two slides were made from each vial using the two filter types yielding two paired slides, one from a cut-frit filter and one from a pressed-frit filter. The transfer efficiency in this study was obtained by counting the numbers of squamous epithelial cells and abnormal cells remaining on the filters as well as using an automated counter, emulating the manual counting recommended by the Bethesda 2001 System, to count the cells on the prepared slides. The results from this study confirmed that for both types of filters, the cell transfer rate was > 95% with a negligible difference between the two types of frits, and less than 1% of the total numbers of cells remaining on either type of filter were abnormal thus demonstrating similar performance for both filter types.

The Control of Cellular Cross Contamination study was designed to assess the risk of cellular contamination or carryover from one specimen to the next. In the validation study, two groups of specimens were run sequentially and alternated with blank vials containing only the MPPT-STC collection fluid. Group one consisted of 15 highly cellular abnormal (LSIL or HSIL) specimens and group two consisted of 10 densely cellular pooled NILM specimens. From group one, all test blanks were free of cellular material and from group two, the final test blank contained one highly degenerated cell of undetermined origin. This study demonstrated that processing cervical specimens on the MPPT system is not affected by cellular cross-contamination that can be detected by microscopic examination.

The objective of the Potential Interference by Extraneous Materials study was to see if any patient-introduced foreign materials interfered with the MPPT slide preparation and diagnosis. The eighteen slides in this study were prepared from specimen pools made from patient specimens previously designated as NILM. Foreign materials (douches, antifungal agent, vaginal lubricants, condom fluid and contraceptive foams) and blood were added to the specimen vials. The slides were reviewed by a cytotechnologist to determine if any of the slides were unsatisfactory using the Bethesda System 2001 guidelines or contained abnormal cells. Abnormal slides were further reviewed by a cytopathologist. The slides were also rated on the subjective slide quality metrics of nuclear and cellular morphology; fixation quality and artifact; and staining. Two of the 18 slides were called unsatisfactory due to obscuring blood and five of the slides contained abnormal cells (ASC-US and LSIL). All seven diagnoses were confirmed by the cytopathologist. It was suggested that one or more of the NILM specimens may have contained a small number of abnormal cells. For the slide quality assessment, most of the slides were rated as satisfactory in all categories. The exceptions are two slides that are rated unsatisfactory and two that are rated superior. This study demonstrated that samples containing the potentially-interfering substances yielded slides that were mostly satisfactory for diagnosis.

B. Additional Studies

Software Verification Test. A software verification test used to test the MonoPrep™ system was submitted by MonoGen, Inc. The software test is based upon incremental phased verification and validation activities for the MonoPrep™ system. The activities consist of methods to (1) verify that the functions provided by the system have been implemented per the specifications; (2) verify the safe operation of the system within its intended use; (3) demonstrate the quality/performance characteristics of the system; and (4) verify the integrity of the data maintained or produced by the system. The Software Reviewer found the software verification test to be adequate.

X. SUMMARY OF CLINICAL STUDIES

A. Clinical Study Design

A prospective, multi-center, masked, split-sample study was conducted in which the objective was to assess MonoPrep Pap Test (MPPT) performance as compared to the conventional Pap smear (PS) for the detection of cervical cancer, pre-cancerous lesions and atypical cells, in subjects representing a spectrum of high, intermediate, and low-risk populations. In addition, an assessment of specimen adequacy, endocervical cells and other analyses was performed. This study used a split-sample design, in which the Pap smear was collected and prepared using FDA-cleared spatula and endocervical cytobrush. The smear residuum remaining on the collection device was then rinsed in the MPPT collection vial which was used to prepare the MPPT slide by the study laboratory. Hence, each case consisted of two slides, one prepared by MPPT and one by PS. MPPT and conventional Pap smear slides were subjected to independent, masked review by the laboratory.

Both MPPT and conventional Pap smear slides of the subjects for whom either the

MPPT or Pap smear slides were diagnosed as Reactive/Reparative or more severe by the study laboratory, and at least 5% of all cases where both slides were diagnosed as NILM-WNL or UNSAT were submitted to one of the five experts, board-certified cytopathologists for masked independent reference review. The review process was used to establish an independent reference diagnosis for each patient for comparing the clinical performance of MPPT to Pap smears.

B. Study Sites

Cervical cytology specimens were collected from 11,244 women in the United States (72 sites) as well as South Africa (11 sites) and Venezuela (2 sites). All specimens were then processed at four U.S sites: CYTO Specialty Laboratories, San Antonio, TX, (Sharon Rosenthal, M.D., Principal Investigator); DCL Medical Laboratory, Indianapolis, IN, (Carol Eisenhut, M.D., Principal Investigator); Pathology Services, Cambridge, MA, (Lynda Rushing, M.D., Principal Investigator); and Universal Diagnostic Laboratories, Brooklyn, NY, (Roosevelt Torno, M.D., Principal Investigator).

The study was conducted at four regional study laboratories. Each laboratory was fully accredited, and all study personnel were required to have documented competence with screening Pap smears and liquid-based Pap tests. Each laboratory typically performs at least 100,000 Pap tests per year. Each laboratory was also required to have at least two certified cytotechnologists and at least one board certified cytopathologist to participate in the study.

A total of 11,244 subjects were enrolled in the study. Of these 11,244, the specimens from 339 (3.0%) were received after the study cutoff date and not processed or evaluated. Of 10,905 subjects whose specimens were accepted for processing and evaluation, 121 (1.1%) were excluded from the statistical analysis due to at least one major protocol violation. There were 45 additional cases in which acetic acid was used for the preparation of the MPPT slides; these cases were also excluded from the statistical analysis of effectiveness. The total number of subjects included in the statistical analysis of effectiveness was 10,739.

Table 1 provides study site demographics; laboratory annual Pap smear and liquid-based Pap test volume; and the number of subjects evaluated at each of the four study labs. In nearly all cases, the matching Pap smear and MPPT specimen were sent to the same laboratory.

Table 1. Study Site Demographics

Site	1	2	3	4
Low Risk Population	88%	82%	90%	94%

High Risk Population	12%	18%	10%	6%
Smear-Based Pap Tests Per Year	21,000	24,400	126,200	310,100
Liquid-Based Pap Tests Per Year	191,700	80,700	54,200	78,300
Number of Cyto technologists in Study	8	5	3	3
Number of Cytopathologists in Study	2	2	1	1
Study Participation Dates	03/01/04 – 10/28/04	03/15/04 – 11/22/04	04/02/04 – 11/26/04	03/31/04 – 12/10/04
Number of Subjects in Study	3045	2147	2119	3428

C. Study Population

Women who met the eligibility requirements were enrolled sequentially at each site. The inclusion criteria were female patients 18 years of age; presence of sufficient cervix to obtain a Pap smear; no physician's contraindication for obtaining a Pap smear; and the ability to provide written informed consent.

Specimens were collected from gynecology medical practices, health clinics, and medical referral centers providing gynecology services to patients representing a spectrum of high to low prevalence populations and diverse ethnic and racial heritage, age and geographical location. These included 75 US and 13 international (11 South African and 2 Venezuelan) collection sites. The following tables present the laboratory and subject information. IRB approved informed consent was obtained from all evaluable subjects. The demographic characteristics of the study population are provided in Table 2 below.

Table 2. Subject Demographics

Subject Demographics	Number	Percent
U.S. Subjects	7,689	72%
International Subjects	3,050	28%
<u>Cervical Risk</u>		
High Risk Subjects	3,513	33%
Abnormal Pap in previous five years	1,610	15%
<u>Race/Ethnic</u>		
White	5,213	49%
Hispanic	2,690	25%
Black	1,400	13%
Other (or not provided)	1,141	11%
Asian	227	2.1%

Indian Pacific	37 31	0.3% 0.3%
Age Mean \pm SD Range	35.4 \pm 12.2 18 to 90	

D. Laboratory Cytology Review

Each laboratory had the participation of at least two screening cytotechnologists, at least one quality-control (QC) cytotechnologist, and at least one board-certified cytopathologist. Pap smear and MonoPrep slides were prepared, screened, and interpreted by the participating laboratories' study cytotechnologists and cytopathologists in the same manner as their routine practice, except in the case of certain protocol procedures intended to maintain consistency across the laboratory sites (e.g., common definition of "high-risk" to be used for selection of cases requiring QC review). All slides were interpreted for the study in accordance with CLIA requirements using TBS2001 nomenclature, including the criteria for a satisfactory slide. All reading of MonoPrep slides was performed independently of Pap smear reviews. Tables 3 and 4 present the comparison of the TBS2001 diagnostic categories for MPPT slides versus conventional Pap smear slides obtained by laboratory cytology review (Lab MPPT vs. Lab PS) for all four sites combined (Table 3) and each site separately (Table 4).

Table 3. Laboratory MPPT Diagnosis vs. Laboratory PS Diagnosis (Combined Sites)

Lab MPPT Dx	Lab PS Dx											
	UNSAT	NILM-WNL	NILM-RR	ASC-US	ASC-H	AGC	LSIL	HSIL	AIS	SCC	AC	Total
UNSAT	43	58	6	12			5	2				126
NILM-WNL	209	7,744	198	459	16	35	55	15			1	8,732
NILM-RR	11	214	59	40	1	1	6	2		1		335
ASC-US	23	538	41	201	4	7	73	7				894
ASC-H	1	9		10			2	2		1		25
AGC	4	21	1	4	1	1	1		1			34
LSIL	6	135	1	112	1		176	27		1		459
HSIL	2	4		10	7	1	22	50		6		102
AIS	1								2			3
SCC	2			1	4			5		13		25
AC								1		2	1	4
Total	302	8,723	306	849	34	45	340	111	3	24	2	10,739

Abbreviation for Diagnoses: UNSAT = Unsatisfactory; NILM-WNL = Negative for Intraepithelial Lesions or Malignancy, Within Normal Limits; NILM-RR = Negative for Intraepithelial Lesions or Malignancy, Reparative/Reactive; ASC-US = Atypical Squamous Cells of Undetermined Significance; ASC-H = Atypical Squamous Cells, cannot exclude HSIL; AGC = Atypical Glandular Cells; LSIL = Low-grade Squamous Intraepithelial Lesion; HSIL = High-grade Squamous Intraepithelial

Lesion; AIS = Adenocarcinoma *in situ*; SCC = Squamous Cell Carcinoma; AC = Adenocarcinoma.

Table 4. Summary Laboratory Diagnosis vs. Site

Site	Method	Lab Dx											Total
		UNSAT	NILM-WNL	NILM-RR	ASC-US	ASC-H	AGC	LSIL	HSIL	AIS	SCC	AC	
1	MPPT	61	2,367	64	245	14	12	195	58	3	22	4	3,045
	PS	120	2,283	45	298	21	13	163	77	3	21	1	3,045
2	MPPT	21	1,684	195	172	4	8	51	11		1		2,147
	PS	74	1,646	201	159	9	13	36	6		2	1	2,147
3	MPPT	33	1,828	76	102	7	2	63	7		1		2,119
	PS	80	1,853	58	75	4	1	41	7				2,119
4	MPPT	11	2,853		375		12	150	26		1		3,428
	PS	28	294	2	317		18	100	21		1		3,428
Combined	MPPT	126	8,732	335	894	25	34	459	102	3	25	4	10,739
	PS	302	8,723	306	849	34	45	340	111	3	24	2	10,739
Grouped Diagnoses	MPPT	UNSAT/NILM (WNL/RR)		9,193	ASCUS+	1,546	LSIL+	593	HSIL+	134	Cancer	32	

E. Reference Diagnosis by the Independent Pathologist

The independent pathology (IP) review panel was composed of five (5) board-certified cytopathologists. The independent pathologists were Marshall Austin, M.D., Costal Pathology Associates, Charleston, SC; David Bolick, M.D., AmeriPath Laboratories, Sandy, UT; Michael Glant, M.D., DCL Medical Laboratories, Indianapolis, IN; Michael Henry, M.D., MIAC, Cleveland Clinic Florida, Naples, FL; and Ann Moriarty, M.D., AmeriPath Laboratories, Indianapolis, IN.

The cases which had either PS or MPPT laboratory diagnoses of NILM-RR and above were designated for IP review. There were 2,690 cases in the study with laboratory

diagnoses of NILM-RR and above on PS and/or MPPT slides; 2,684 cases (99.8%) were referred to the panel. In addition, 508 cases (6.3%) randomly selected from the 8,094 cases that were diagnosed at the laboratories as NILM-WNL or UNSAT on both PS and MPPT were referred for IP review.

Each of the slides in the referred cases was separately randomized to one of the five cytopathologists for review. Randomization was independently performed for MPPT and PS, and for slides from each site to ensure a balanced random allocation of slides among the five reference cytopathologists. The two slides were reviewed by the reference pathologists for 3,192 referred cases. Each slide was masked as to the laboratory diagnosis for either slide in the case. Seven (7) cases, for which acetic acid was used to reprocess the MPPT slides, were excluded from the statistical analysis. The distribution of the 3,185 cases reviewed by an independent pathologist and available for statistical analysis is presented by Table 5. Each cell of the table presents the total number of cases and the number of cases reviewed by Independent Pathologist ("IP").

Table 5. Distribution of Cases Reviewed by Independent Pathologist

		PS Lab Dx				Total
		UNSAT	NILM-WNL	NILM-RR	ASC-US+	
MPPT Lab Dx	UNSAT	43	58	6	19	126
		IP: 1	IP: 1	IP: 6	IP: 19	IP: 27
	NILM-WNL	209	7,744	198	581	8,732
		IP: 13	IP: 491	IP: 198	IP: 580	IP: 1,282
	NILM-RR	11	214	59	51	335
		IP: 11	IP: 211	IP: 58	IP: 51	IP: 331
	ASC-US+	39	707	43	757	1,546
		IP: 39	IP: 706	IP: 43	IP: 757	IP: 1,545

For each IP-reviewed case (3,185 in all), the reference diagnosis was recorded as the more severe diagnosis rendered from the MPPT and PS slides by an Independent Pathologist. This result was used as the cytological "truth" diagnosis for the case or Reference Diagnosis by Independent Pathologist ("Reference Diagnosis", or RDIP). To assess the performance of the MPPT relative to conventional Pap smear for each IP-reviewed case, the laboratory diagnoses made by the study site using the two methods were compared to the RDIP.

Table 6. Independent Pathologist MPPT Diagnosis vs. Independent Pathologist PS Diagnosis (Combined Sites)

IP MPPT Dx	IP PS Dx											
	UNSAT	NILM-WNL	NILM-RR	ASC-US	ASC-H	AGC	LSIL	HSIL	AIS	SCC	AC	Total
UNSAT	26	24	8	11	4	1	5	3			1	83
NILM-WNL	100	568	174	162	17	3	36	14				1,074
NILM-RR	62	217	104	93	14	4	23	11				528
ASC-US	67	248	89	131	22	2	56	17			1	633
ASC-H	11	27	18	12	6	1	8	6				89
AGC	1	13	3	3	2		1	1		1		25
LSIL	35	136	34	116	6		153	13		1		494
HSIL	8	38	18	50	8	1	28	66	1	5		223
AIS	1	1							1			3
SCC	7		1	1	2			9		10	1	31
AC					1						1	2
Total	318	1,272	449	579	82	12	310	140	2	17	4	3,185

In the clinical study, there were 46 cases with Reference Diagnosis of Cancer (Adenocarcinoma, Squamous Cell Carcinoma, or AIS); 328 cases with Reference Diagnosis of HSIL+; 937 cases with Reference Diagnosis of LSIL+; 1,101 cases with Reference Diagnosis of ASC-H+; and 1,902 cases with Reference Diagnosis of ASC-US+.

F. Outcome Measures

MonoPrep Pap Test screening performance was compared to Pap smear by assessing the relative detection of cervical abnormalities and other conditions, as defined in *The Bethesda System 2001* (TBS2001). Clinical sensitivity and specificity (e.g., with reference to a histological diagnosis) cannot be measured in this study, which relied on cytological examination alone. Rendering RDIPs based on examination of each slide by only one pathologist likely increased the variability inherent in the RDIPs. Another complicating factor is that the IP diagnosis from the MPPT slide (i.e. from the device under testing), was used to establish the Reference Diagnosis for some cases.

Instead of comparing sensitivity and specificity, laboratory true positive and false positive diagnoses by both methods, MPPT and PS, were compared for the cases with a Reference Diagnosis by the Independent Pathologists (RDIP) of ASC-US+, ASC-H/AGC+, LSIL+, HSIL+ and cancer were compared. The prospectively designed primary objective was to demonstrate that MPPT provides a statistically significant improvement over screening with Pap smears for the detection of cases with RDIP-confirmed ASC-US+ and LSIL+ cases. (See Section G. for details.)

About 6% of the cases with both PS and MPPT results of NILM-WNL were referred for RDIP. A result is that the data set of the 3,185 cases with RDIP necessarily has a statistical verification bias because only random sample of cases with both PS and MPPT results of NILM-WNL are submitted for RDIP⁽²⁾. Despite this verification bias, the ratio of true positive rates by the two methods and the ratio of false positive

rates by the two methods are unbiased⁽³⁾. For the various comparisons made below, true positive results are those for which a positive laboratory diagnosis is matched by a positive RDIP. Results without such a match were false positive. The ratios of true positive rates (TPR_{MPPT}/TPR_{PS}) and ratios of false positives rates (FPR_{MPPT}/FPR_{PS}) and their 95% confidence intervals were calculated for the cases with Reference Diagnosis of ASC-US+, ASC-H+/AGC+, LSIL+, HSIL+, and cancer. Because of the split-sample design, the positive rates of PS and MPPT were correlated and the false positive rates of PS and MPPT were also correlated. In order to address properly the correlation structure in the calculation of 95% confidence intervals for the ratio of positive rates of MPPT and PS and for the ratio of false positive rates of MPPT and PS, a bootstrap technique was used. The statistical significance of ratios differing from 1.0 was demonstrated when the 95% confidence interval did not include 1.0.

G. Clinical Study Data Results and Analysis

Tables 7 through 11 present the comparison of laboratory true positive and false positive rates for ASC-US+ (Table 7); ASC-H+/AGC+ (Table 8); LSIL+ (Table 9); HSIL+ (Table 10) and Cancer (Table 11). Tables present the number of RDIP positive and negative cases for each cutoff, the number of positive and negative laboratory results, and their ratio. These data are presented for each site, and include the 95%CI of the ratio for the pooled result of all sites for each cutoff. Data for each site are presented to illustrate the degree of consistency of the results across all sites.

ASC-US+

Table 7. Laboratory MPPT Results Versus Laboratory PS Results for the Cases with Reference Diagnosis by Independent Pathologist of ASC-US+

Site	Cases Pos. by IP	MPPT Pos.	PS Pos.	Ratio TPR_{MPPT}/TPR_{PS}	Cases Non-Pos. by IP	MPPT Pos.	PS Pos.	Ratio FPR_{MPPT}/FPR_{PS}
Site 1	702	489	479	1.02	361	64	117	0.55
Site 2	303	163	135	1.21	535	83	91	0.91
Site 3	272	171	115	1.49	105	11	13	0.85
Site 4	625	451	382	1.18	282	113	75	1.51
Combined (95% CI)	1,902	1,274	1,111	1.15 (1.09; 1.20)	1,283	271	296	0.92 (0.77; 1.06)

In this table, "Positive" means "ASC-US+" (combined ASC-US, ASC-H, AGC, LSIL, HSIL, and Cancer) and "Non-Positive" means "Non-ASC-US+" (combined NILM-RR, NILM-WNL, and UNSAT).

The results presented in Table 7 show that for the cases with a Reference Diagnosis of ASC-US+, the MPPT method detected 1.15 (1,274/1,111) times more true positive cases than the PS method detected, for all sites combined. This increase was statistically significant, with the lower limit of the 95% confidence interval at 1.09. The observed ratios of the true positive rates varied among the sites from 1.02 to 1.49.

The ratio of the false positive rates was 0.92 (271/296), for all sites combined. The observed decrease in the false positive MPPT rate relative to the false positive PS rate was not statistically significant with 95% confidence interval of 0.77 to 1.06.

In order to make a conclusion about the equivalence of the false positive rates, a multiple imputation⁽⁴⁾ was performed for obtaining the unbiased estimate of the difference between MPPT and PS false positive rates. The difference between MPPT and PS false positive rates was -0.3% with 95% CI: -0.86% to 0.26%. The criteria for the equivalence of false positive rates of MPPT and PS for ASC-US+ with delta = 0.5% for the difference of MPPT and PS false positive rates was met (the upper limit of 0.26% is below 0.5%).

ASC-H/AGC+

Table 8. Laboratory MPPT Results Versus Laboratory PS Results for the Cases with Reference Diagnosis by Independent Pathologist of ASC-H/AGC+.

Site	Cases Pos. by IP	MPPT Pos.	PS Pos.	Ratio $\frac{TPR_{MPPT}}{TPR_{PS}}$	Cases Non-Pos. by IP	MPPT Pos.	PS Pos.	Ratio $\frac{FPR_{MPPT}}{FPR_{PS}}$
Site 1	444	274	247	1.11	619	34	52	0.65
Site 2	131	49	43	1.14	707	26	24	1.08
Site 3	159	75	45	1.67	218	5	8	0.63
Site 4	367	139	103	1.35	540	50	37	1.35
Combined (95% CI)	1,101	537	438	1.23 (1.13; 1.32)	2,084	115	121	0.95 (0.72; 1.18)

In this table, "Positive" means "ASC-H/AGC+" (combined ASC-H, AGC, LSIL, HSIL, and Cancer) and "Non-Positive" means "Non-ASC-H/AGC+" (combined ASC-US, NILM-RR, NILM-WNL, and UNSAT).

The results presented in Table 8 above show that for the cases with a Reference Diagnosis of ASC-H/AGC+, the MPPT method detected 1.23 (537/438) times more true positive cases than the PS method detected, for all sites combined. This increase was statistically significant with the lower limit of the 95% confidence interval at 1.13. The observed ratios of the positive rates varied among the sites from 1.11 to 1.67.

The ratio of the false positive rates was 0.95 (115/121) for all sites combined. The observed decrease in the false positive MPPT rate relative to the false positive PS rate was not statistically significant with 95% confidence interval of 0.72 to 1.18. In order to make a conclusion about the equivalence of the false positive rates, a multiple imputation was performed for obtaining the unbiased estimate of the difference between MPPT and PS false positive rates. The difference between MPPT and PS false positive rates was -0.05% with 95% CI: -0.34% to 0.24%. The criteria for the equivalence of false positive rates of MPPT and PS for ASC-H+ with delta = 0.5% for the difference of MPPT and PS false positive rates was met (the upper limit of 0.24% is below 0.5%).

LSIL+

Table 9. Laboratory MPPT Results Versus Laboratory PS Results for the Cases with Reference Diagnosis by Independent Pathologist of LSIL+.

Site	Cases Pos. by IP	MPPT Pos.	PS Pos.	Ratio $\frac{TPR_{MPPT}}{TPR_{PS}}$	Cases Non-Pos. by IP	MPPT Pos.	PS Pos.	Ratio $\frac{FPR_{MPPT}}{FPR_{PS}}$
Site 1	388	250	220	1.14	675	32	45	0.71
Site 2	97	43	32	1.34	741	20	13	1.54
Site 3	141	66	43	1.53	236	5	5	1.00
Site 4	311	127	90	1.41	596	50	32	1.56
Combined (95% CI)	937	486	385	1.26 (1.16; 1.36)	2,248	107	95	1.13 (0.84; 1.41)

In this table, "Positive" means "LSIL+" (combined LSIL, HSIL, and Cancer) and "Non-Positive" means "Non-LSIL+" (combined AGC, ASC-H, ASC-US, NILM-RR, NILM-WNL, and UNSAT).

The results presented in Table 9 show that for the cases with a Reference Diagnosis of LSIL+, the MPPT method detected 1.26 (486/385) times more true positive cases than the PS method detected, for all sites combined. This increase was statistically significant with the lower limit of the 95% confidence interval at 1.16. The observed ratios of the positive rates varied among the sites from 1.14 to 1.53.

The ratio of the false positive rates was 1.13 (107/95) for all sites combined. The observed increase in the false positive MPPT rate relative to the false positive PS rate was not statistically significant with 95% confidence interval of 0.84 to 1.41. In order to make a conclusion about the equivalence of the false positive rates, a multiple imputation was performed for obtaining the unbiased estimate of the difference between MPPT and PS false positive rates. The difference between MPPT and PS false positive rates was +0.1% with 95% CI: -0.15% to 0.35%. The criteria for the equivalence of false positive rates of MPPT and PS for ASC-H/AGC+ with delta = 0.5% for the difference of MPPT and PS false positive rates was met (the upper limit of 0.35% is below 0.5%).

HSIL+

Table 10. Laboratory MPPT Results Versus Laboratory PS Results for the Cases with Reference Diagnosis by Independent Pathologist of HSIL+.

Site	Cases Pos. by IP	MPPT Pos.	PS Pos.	Ratio $\frac{TPR_{MPPT}}{TPR_{PS}}$	Cases Non-Pos. by IP	MPPT Pos.	PS Pos.	Ratio $\frac{FPR_{MPPT}}{FPR_{PS}}$
Site 1	156	79	82	0.96	908	8	20	0.40
Site 2	32	8	6	1.33	806	4	2	1.33
Site 3	31	7	6	1.17	346	1	1	1.00
Site 4	109	19	15	1.27	798	8	7	1.14
Combined (95% CI)	328	113	109	1.04 (0.88; 1.19)	2,857	21	31	0.68 (0.33; 1.02)

In this table, "Positive" means "HSIL+" (combined HSIL, and Cancer) and "Non-Positive" means "Non-HSIL+" (combined LSIL, AGC, ASC-H, ASC-US, NILM-RR, NILM-WNL, and UNSAT).

The results presented in Table 10 show that for the cases with a Reference Diagnosis of HSIL+, the MPPT method detected 1.04 (113/109) times more true positive cases than the PS method detected, for all sites combined. This increase was not statistically significant with the 95% confidence interval of 0.88 to 1.19. A multiple imputation technique provided the unbiased point estimate of difference MPPT and PS true positive rates of 0.9% with 95% CI: -3.7% to 5.4%. The criteria for the equivalence of true positive rates of MPPT and PS for HSIL+ with delta = -5.0% for the difference of MPPT and PS positive rates was met (the lower limit of -3.7% is above -5.0%). The observed ratios of the positive rates varied among the sites from 0.96 to 1.33.

The ratio of the false positive rates was 0.68 (21/31) for all sites combined. The observed decrease in the false positive MPPT rate relative to the false positive PS rate was not statistically significant with a 95% confidence interval of 0.33 to 1.02. In order to make a conclusion about the equivalence of the false positive rates, a multiple imputation was performed for obtaining the unbiased estimate of the difference between MPPT and PS false positive rates. The difference between MPPT and PS false positive rates was -0.08% with 95% CI: -0.20% to 0.04%. The criteria for the equivalence of false positive rates of MPPT and PS for ASC-H/AGC+ with delta = 0.5% for the difference of MPPT and PS false positive rates was met (the upper limit of 0.04% is below 0.5%).

Cancer

Table 11. Laboratory MPPT Results Versus Laboratory PS Results for the Cases with Reference Diagnosis by Independent Pathologist of Cancer.

Site	Cases Pos. by IP	MPPT Pos.	PS Pos.	Ratio $\frac{TPR_{MPPT}}{TPR_{PS}}$	Cases Non-Pos. by IP	MPPT Pos.	PS Pos.	Ratio $\frac{FPR_{MPPT}}{FPR_{PS}}$
Site 1	40	26	21	1.24	1,023	3	4	0.75
Site 2	1	0	1	0.0	837	1	2	0.5
Site 3	1	1	0	n/a	376	0	0	n/a
Site 4	4	1	1	1.0	903	0	0	n/a
Combined (95% CI)	46	28	23	1.22 (0.87; 1.75)	3,139	4	6	0.66

In this table, "Positive" means "Cancer" (combined AIS, Squamous Cell Carcinoma, and Adenocarcinoma) and "Non-Positive" means "Non-Cancer" (combined HSIL, LSIL, AGC, ASC-H, ASC-US, NILM-RR, NILM-WNL, and UNSAT).

The results presented in Table 11 show that for the cases with a Reference Diagnosis of Cancer, the MPPT method detected 1.22 (28/23) times more true positive cases than the PS method detected, for all sites combined. This increase was not statistically significant with the 95% confidence interval of 0.87 to 1.75. The ratio of the false positive rates was 0.66 (4/6) for all sites combined. The observed decrease in the false positive MPPT rate relative to the false positive PS rate was not statistically significant.

H. LABORATORY MPPT VERSUS PAP SMEAR RESULTS FOR INDIVIDUAL REFERENCE DIAGNOSIS BY INDEPENDENT PATHOLOGIST CATEGORY

Tables 12-19 show the comparison of the laboratory MPPT diagnosis and laboratory PS diagnosis for the cases with the following Reference Diagnoses: NILM-WNL, NILM-RR, ASC-US, ASC-H, AGC, LSIL, HSIL and Cancer (Adenocarcinoma, Squamous Cell Carcinoma, or AIS) separately. This comparison illustrates the diversity of laboratory results with MPPT and Pap smear method for each Reference Diagnosis. An IP diagnosis was made for each slide, and may or may not be the same within a case. The Reference Diagnosis by Independent Pathologist was the most severe of the two IP diagnoses.

NILM-WNL

Table 12. Cases with Reference Diagnosis of NILM-WNL

Lab MPPT Dx	Lab PS Dx											Total
	UNSAT	NILM- WNL	NILM- RR	ASC- US	ASC- H	AGC	LSIL	HSIL	AIS	SCC	AC	
UNSAT		1	1	3								5
NILM-WNL	5	310	69	93	3	7	6					493
NILM-RR	4	58	18	8			1					89
ASC-US	1	82	3	10		1						97
ASC-H		2										2
AGC		2										2
LSIL		4										4
HSIL												
AIS												
SCC												
AC												
Total	10	459	91	114	3	8	7					692

Among the 692 cases with a Reference Diagnosis of NILM-WNL, 493 (71.2%) cases had a laboratory MPPT diagnosis of NILM-WNL and 459 cases (66.3%) had a laboratory PS diagnosis of NILM-WNL; 4 cases (0.6%) had a laboratory MPPT diagnosis of LSIL+ and 7 (1.0%) cases had a laboratory PS diagnosis of LSIL+.

NILM-RR

Table 13. Cases with Reference Diagnosis of NILM-RR

Lab MPPT Dx	Lab PS Dx											Total
	UNSAT	NILM- WNL	NILM- RR	ASC- US	ASC- H	AGC	LSIL	HSIL	AIS	SCC	AC	
UNSAT			3				2					5
NILM-WNL	3	95	75	102	4	10	8	1				298
NILM-RR	5	72	20	10								107
ASC-US	5	105	10	9	1	1	3					134
ASC-H				1								1
AGC		5	1	1								7
LSIL	1	10		1								12
HSIL					1							1
AIS												
SCC												
AC												
Total	14	287	109	124	6	11	13	1				565

Among the 565 cases with a Reference Diagnosis of NILM-RR, 107 (18.9%) cases had a laboratory MPPT diagnosis of NILM-RR and 109 cases (19.3%) had a laboratory PS diagnosis of NILM-RR; 13 cases (2.3%) had a laboratory MPPT diagnosis of LSIL+ and 14 (2.5%) cases had a laboratory PS diagnosis of LSIL+.

ASC-US

Table 14. Cases with Reference Diagnosis of ASC-US

Lab MPPT Dx	Lab PS Dx											Total
	UNSAT	NILM- WNL	NILM- RR	ASC- US	ASC- H	AGC	LSIL	HSIL	AIS	SCC	AC	
UNSAT	1			2			2	1				6
NILM-WNL		58	45	163	7	6	20					299
NILM-RR	2	53	11	12			2					80
ASC-US	7	211	15	79	1	2	15	1				331
ASC-H		1		3								4
AGC	1	5										6
LSIL		34	1	25			9	3				72
HSIL		1		1	1							3
AIS												
SCC												
AC												
Total	11	363	72	285	9	8	48	5				801

Among the 801 cases with a Reference Diagnosis of ASC-US, 416 (51.9%) cases had a laboratory MPPT diagnosis of ASC-US+ and 355 cases (44.3%) had a laboratory PS diagnosis of ASC-US+; 379 cases (47.3%) had a laboratory MPPT diagnosis of NILM and 435 (54.3%) cases had a laboratory PS diagnosis of NILM.

ASC-H

Table 15. Cases with Reference Diagnosis of ASC-H

Lab MPPT Dx	Lab PS Dx											Total
	UNSAT	NILM- WNL	NILM- RR	ASC- US	ASC- H	AGC	LSIL	HSIL	AIS	SCC	AC	
UNSAT			2	2								4
NILM-WNL	1	13	8	21	2	2	3	5				55
NILM-RR		8	5	1	1		1					16
ASC-US		21	2	10		1	4	1				39
ASC-H		1						1				2
AGC				1								1
LSIL		6		4				2				12
HSIL								1				1
AIS									1			1
SCC												
AC												
Total	1	49	17	39	3	3	8	10	1			131

Among the 131 cases with a Reference Diagnosis of ASC-H, 17 (13.0%) cases had a laboratory MPPT diagnosis of ASC-H+ and 25 cases (19.1%) had a laboratory PS diagnosis of ASC-H+; 71 cases (54.2%) had a laboratory MPPT diagnosis of NILM

and 66 (50.4%) cases had a laboratory PS diagnosis of NILM.

AGC

Table 16. Cases with Reference Diagnosis of AGC

Lab MPPT Dx	Lab PS Dx											Total
	UNSAT	NILM- WNL	NILM- RR	ASC- US	ASC- H	AGC	LSIL	HSIL	AIS	SCC	AC	
UNSAT												
NILM-WNL		8		4		3	1					16
NILM-RR		3	2									5
ASC-US		5			1							6
ASC-H												
AGC		2		1	1				1			5
LSIL				1								1
HSIL												
AIS												
SCC												
AC												
Total		18	2	6	2	3	1		1			33

Among the 33 cases with a Reference Diagnosis of AGC, 6 (18.2%) cases had a laboratory MPPT diagnosis of ASC-H+ and 7 cases (21.2%) had a laboratory PS diagnosis of ASC-H+; 21 cases (63.6%) had a laboratory MPPT diagnosis of NILM and 20 (60.6%) cases had a laboratory PS diagnosis of NILM.

LSIL

Table 17. Cases with Reference Diagnosis of LSIL

Lab MPPT Dx	Lab PS Dx											Total
	UNSAT	NILM- WNL	NILM- RR	ASC- US	ASC- H	AGC	LSIL	HSIL	AIS	SCC	AC	
UNSAT				1			1	1				3
NILM-WNL		3		49			16	2				70
NILM-RR		7		6			1					14
ASC-US	4	89	8	72	1	1	44	1				220
ASC-H		1		2			1					4
AGC	1	1										2
LSIL	3	69		61	1		140	7				281
HSIL				3	1		9	2				15
AIS												
SCC												
AC												
Total	8	170	8	194	3	1	212	13				609

Among the 609 cases with a Reference Diagnosis of LSIL, 296 (48.6%) cases had a laboratory MPPT diagnosis of LSIL+ and 225 cases (36.9%) had a laboratory PS

diagnosis of LSIL+; 84 cases (13.8%) had a laboratory MPPT diagnosis of NILM and 178 (29.2%) cases had a laboratory PS diagnosis of NILM.

HSIL

Table 18. Cases with Reference Diagnosis of HSIL

Lab MPPT Dx	Lab PS Dx											Total
	UNSAT	NILM- WNL	NILM- RR	ASC- US	ASC- H	AGC	LSIL	HSIL	AIS	SCC	AC	
UNSAT				1								1
NILM-WNL		2	1	22		5	1	7				38
NILM-RR		10	2	2			1	2				17
ASC-US	2	19	2	21		1	7	4				56
ASC-H		4		4			1	1				10
AGC	1	5		1			1					8
LSIL	2	12		20			27	15				76
HSIL	2	3		6	4		13	42		3		73
AIS												
SCC								2		1		3
AC												
Total	7	55	5	77	4	6	51	73		4		282

Among the 282 cases with a reference diagnosis of HSIL, 76 (27.0%) cases had a laboratory MPPT diagnosis of HSIL+ and 77 cases (27.3%) had a laboratory PS diagnosis of HSIL+; 55 cases (19.5%) had a laboratory MPPT diagnosis of NILM and 60 (21.3%) cases had a laboratory PS diagnosis of NILM.

CANCER

Table 19. Cases with Reference Diagnosis of Cancer (Adenocarcinoma, Squamous Cell Carcinoma, or AIS)

Lab PS Dx												
Lab MPPT Dx	UNSAT	NILM-WNL	NILM-RR	ASC-US	ASC-H	AGC	LSIL	HSIL	AIS	SCC	AC	Total
UNSAT				1		0						1
NILM-WNL						1					1	2
NILM-RR										1		1
ASC-US												
ASC-H	1									1		2
AGC		1				1						2
LSIL										1		1
HSIL						1		5		3		9
AIS	1								1			2
SCC	2			1	4			3		12		22
AC								1		2	1	4
Total	4	1		2	4	3		9	1	20	2	46

Among the 46 cases with a Reference Diagnosis of Cancer (Adenocarcinoma, Squamous Cell Carcinoma, or AIS), 37 (80.4%) cases had a laboratory MPPT diagnosis of HSIL+ and 32 (69.6%) cases had a laboratory PS diagnosis of HSIL+; 3 (6.5%) cases had a laboratory MPPT diagnosis of NILM, and 1 (2.2%) case had a laboratory PS diagnosis of NILM.

Twenty-eight (60.9%) of the 46 cases had a laboratory MPPT diagnosis of Cancer and 23 (50.0%) had a laboratory PS diagnosis of Cancer. None of the 46 (0.0%) cases had a MPPT IP diagnosis of NILM (WNL or RR); 2 (4.3%) had a PS IP diagnosis of NILM (WNL or RR).

For the three cases with a MPPT Laboratory diagnosis of NILM, none were NILM by IP diagnosis of that slide. In one case, the IP diagnosis for cancer was made only on the MPPT slide, with the Pap smear IP diagnosis being UNSAT. In an additional post-study review by two study cytopathologists, the MPPT slide was considered extremely difficult to diagnose because of cytolysis with poor preservation and pre-collection necrosis. There were cells suggestive of atypical repair. The PS slide was thick, air dried, and poorly preserved "except for sprinkling of well preserved atypical keratinizing cells suggestive of squamous carcinoma."

The second case was cancer by IP diagnosis for the Pap smear, though AGC by the laboratory diagnosis of that slide. The MonoPrep laboratory diagnosis was NILM, with only the primary screening cytotechnologist review, without QC review. The MPPT IP diagnosis was ASC-US. In an additional post-study review by two study cytopathologists, the abnormal cells in the Pap smear were considered diagnostically difficult, consistent with either endometrial adenocarcinoma or endometrial AGC. For the MPPT slide, the secondary reviewing cytopathologists concurred that "rare small atypical groups" were present.

The third case's IP diagnoses were cancer for the Pap smear and UNSAT for the MPPT slide. The MonoPrep laboratory diagnosis was NILM, with only primary screening cytotechnologist review and no QC review. In an additional post-study review by two

study cytopathologists, both slides were considered very difficult cases, with the Pap smear being UNSAT except for the identification of a "few isolated individual clearly malignant cells buried in the blood." On extensive review "some isolated but poorly preserved similar cells" were identified on the MPPT slide.

For the case with a Laboratory PS diagnosis of NILM (WNL or RR), the PS IP diagnosis was NILM (WNL or RR), while MPPT IP diagnosis was Cancer and Laboratory MPPT diagnosis was AGC. At the laboratory, the PS slide was reviewed and diagnosed as NILM-WNL by both primary and Senior (QC) Cytotechnologists. This case was not part of the post-study slides review.

I. Specimen Adequacy

Table 20 shows results from a comparison of preparation adequacy for the conventional PS and MPPT methods as reviewed by the laboratory for all sites combined and each site separately:

Table 20. Specimen Adequacy Findings

	Lab PS			
		UNSAT	SAT	Total
Lab MPPT	UNSAT	43	83	126
	SAT	259	10,354	10,613
	Total	302	10,437	10,739
Lab				
Site	Method	UNSAT	Total Number of Slides	%UNSAT
1	MPPT	61	3,045	2.0%
	PS	120	3,045	3.9%
2	MPPT	21	2,147	1.0%
	PS	74	2,147	3.4%
3	MPPT	33	2,119	1.6%
	PS	80	2,119	3.8%
4	MPPT	11	3,428	0.3%
	PS	28	3,428	0.8%
Combined	MPPT	126	10,739	1.2%
	PS	302	10,739	2.8%

The estimated unsatisfactory slide rates observed in the laboratories (i.e., without confirmation by independent pathologist (IP)) for the MPPT method were lower than for the PS method (1.2% vs. 2.8%). However, these estimates take no account of MPPT slides that might not have been recognized at the laboratories as unsatisfactory. Few (15) slide pairs with laboratory diagnoses confined to UNSAT or NILM-WNL were sent for IP review (see Table 5), including 13 pairs called UNSAT by PS and NILM-WNL by MPPT. Four MPPT slides from these 13 pairs were categorized as UNSAT by the IP. The number of these slide pairs, and the even smaller number of IP-reviewed pairs called UNSAT by MPPT and NILM-WNL by PS, make evaluation of this finding inconclusive.

J. Abundance of Endocervical / Transformation Zone Component

Laboratories assessed slides for the presence of endocervical and transformation zone component. In the split-sample study, MPPT slides demonstrated no statistically significant difference in abundance of Endocervical/Transformation zone component compared with the matching Pap smear slides as shown in Table 21. ECC/Tz were absent in fewer MPPT than PS slides, but the difference was not statistically significant (-3.3%, 95%CI: -4.0% to 11.0%).

Table 21. Cross-Tabulation of Endocervical and Transformation Zone Component

	Pap Smear			
	Diagnosis	Absent	Detectable	Total
	Absent	640	606	1,246
	Detectable	649	8,604	9,253
	Total	1,289	9,210	10,499

K. Abundance of Abnormal Cells

Laboratories also were asked to assess the relative abundance of abnormal/reactive cells in cases identified as abnormal/reactive. The categories were Abundant (>25) Typical (11-25), and Detectable (1-10). Table 22 presents the comparison for cases where both slides were abnormal/reactive. As shown by the results, there were no statistically significant differences in the abundance of such cells. This demonstrates that MonoPrep presents, on average, at least as many abnormal/reactive cells as a Pap smear, even when made from a split specimen.

Table 22. Cross-Tabulation of Abnormal Cell Abundance

	Pap Smear					
	Abundance	Abundant (>25)	Typical (11-25)	Detectable (1-10)	Total	Row % Cases
	Abundant (>25)	121	74	29	224	31%
	Typical (11-25)	83	116	82	281	39%
	Detectable (1-10)	25	73	113	211	29%
	Total	229	263	224	716	100%
	Col. % of Cases	32%	32%	31%	100%	

L. Detection of Infectious Organisms, Reactive/Reparative and Other Benign Conditions

Screening with MPPT and Pap smear slides presented no statistically significant difference in detection of benign, reactive/reparative conditions and infectious agents. Table 23 shows the detection rates for these conditions and agents.

Table 23. Summary Table Summary of Benign Conditions: MPPT versus PS

Condition	MonoPrep (n=10,739)		Pap Smear (n=10,739)	
	n	%	n	%
Reactive / Reparative	335	3.1%	306	2.8%
Inflammation	249	2.3%	231	2.2%
IUD	0	0.0%	4	0.0%
Atrophic Vaginitis	0	0.0%	1	0.0%
Radiation	3	0.0%	1	0.0%
Other*	67	0.6%	77	0.7%
Infectious Agent	1,507	14.0%	1,496	13.9%
Candida / Fungus	523	4.8%	426	4.0%
Trichomonas Vaginalis	105	1.0%	158	1.5%
Actinomyces	0	0.0%	0	0.0%
Bacterial Vaginosis / Coccobaccilli	980	9.1%	1,035	9.6%
Herpes Simplex	3	0.0%	9	0.1%
Other**	0	0.0%	2	0.0%
* includes unusual observations, such as those resulting from chemical irritation, drug reactions, or cervical trauma.				
**includes appearance of microbial infection or sequela of unidentified or unusual taxonomy				

XI. CONCLUSIONS DRAWN FROM THE STUDIES

For all sites combined, slides prepared by MPPT, compared to PS slides, yielded statistically significant increases in true positive cytological results for the following diagnostic classes: ASC-US+ (1.15, 95%CI: 1.09 to 1.20); ASC-H/AGC+ (1.23, 95%CI: 1.13 to 1.32); and LSIL+ (1.26, 95%CI: 1.16 to 1.36). Hence the increases in true positive yield were at least 9% for ASCUS+, 13% for ASC-H/AGC+, and 16% for LSIL+.

Comparisons of false positive rates did not show a statistically significant difference between MPPT and PS for ASC-US+, ASC-H/AGC+ or LSIL+.

For all sites combined, slides prepared by MPPT, compared to PS slides, did not yield statistically significant differences in true positive or false positive cytological results for the following diagnostic classes: HSIL+ (1.04, 95%CI: 0.88 to 1.19); and Cancer (1.22, 95%CI: 0.87 to 1.75).

Presentation of endocervical cell and transformation zone component, abnormal cells and benign conditions showed no statistically significant difference between MPPT and PS slides.

The data from the clinical trial and clinical support studies demonstrate that the MPPT system is safe and effective for preparing gynecologic cytology slides to screen for cervical abnormalities.

VALIDITY OF THE CLINICAL DATA

The clinical investigation constituted valid scientific evidence as defined in 21 CFR 860.7. The investigation was well-controlled in that a test article and a control article were made from each study subject's cervical sample. This was possible by using a split-sample collection methodology in which a conventional Pap smear was made first, and then the collection devices were rinsed in the MonoGen Specimen Transport Solution. The MonoPrep Pap Test slide was then made from the sample in the Specimen Transport Solution.

The clinical investigation protocol included a statement of the objectives and hypotheses of the study. Statistical testing was based on these pre-defined hypotheses. The clinical study sites were monitored by an independent Contract Research Organization to assure adherence to the protocol.

The statistical methods used to analyze the data from this investigation were based on the estimation of the ratios of true positive rates of MPPT and PS with 95% confidence interval and estimation of the ratios of false positive rates of MPPT and PS with 95% confidence intervals. These estimations were performed for all basic cytological categories: ASC-US+, ASC-H/AGC+, LSIL+, and HSIL+.

RISK BENEFIT ANALYSIS

Specimen preparation errors may result in false negative or false positive diagnoses. A false negative diagnosis may result when there are no abnormal cells on the slide when disease is actually present. False negative diagnoses result in delayed diagnosis and treatment for the patient. A false positive diagnosis may result when normal cells appear abnormal due to faulty slide preparation but no disease is present. As a result the patient may have an unnecessary colposcopy exam (a non-invasive procedure) or may be referred for biopsy (an invasive procedure).

Based on the information in the studies provided, the FDA has concluded that the benefits of using the MonoPrep Pap Test system for its intended use outweigh the risks associated with using it.

SAFETY

The MonoGen MonoPrep Pap Test system is an *in vitro* diagnostic test and does not contact the patient. Instructions for the safe use of the product are included in the package insert.

EFFECTIVENESS

The data from the clinical trial and clinical support studies demonstrate that the MonoGen MonoPrep Pap Test is effective for preparing gynecologic cytology slides to screen for cervical abnormalities.

XII. PANEL RECOMMENDATION

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Hematology and Pathology Devices panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CDRH DECISION

CDRH issued an approval order on March 3, 2006.

The applicant's manufacturing and control facilities were inspected on 9/8/05 and the facilities were found to be in compliance with the Quality System Regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See the labeling (Attachment 1).

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions and Adverse Events in the labeling.

Postapproval Requirements and Restrictions: CDRH approval of this PMA is subject to full compliance with the conditions of approval and post-approval clinical studies described in the approval order (Attachment 2).

XV. REFERENCES

1. Solomon, D et al. The 2001 Bethesda System: terminology for reporting results of cervical cytology. *JAMA*. 2002; 287(16): 2114-19.
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3. Schatzkin, A., Connor, R.J., Taylor, P.R., and Bunnag, B. Comparing new and old screening tests when a reference procedure cannot be performed on all screeners". *American Journal of Epidemiology*, Vol. 125, N.4, p.672-678 (1987).
4. Schafer, J.L. "Multiple Imputation: a Primer". *Statistical Methods in Medical Research*; 8:3-15 (1999).