

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name: Automated Cervical Cytology Screening and Imaging System

Device Trade Name: BD FocalPoint™ GS Imaging System

Applicant's Name and Address: BD Diagnostics,
Diagnostics Systems, TriPath
4025 Stirrup Creek Drive, Suite 400
Durham, NC 27703

Date of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P950009/S008

Date of Notice of Approval to Applicant: December 3, 2008

Expedited: Not applicable

The original PMA (P950009) for the AutoPap 300 QC System was approved on September 29, 1995 and is indicated for use in the quality control and rescreening of previously screened Papanicolaou (Pap) smear slides.

The AutoPap® Primary Screening System (P950009/S002) was approved on May 5, 1998 and is indicated as an automated cervical cytology screening device intended for use in initial screening of Pap smear slides. This system identifies up to 25% of successfully processed slides as requiring no further review and also identifies at least 15% of all successfully processed slides for a second manual review.

The AutoPap® Primary Screening System (P950009/S004) was approved on November 5, 2001 and is indicated as an automated cervical cytology screening device intended for use in initial screening of both conventionally-prepared Pap smear slides and AutoCyte PREP liquid-based slides. This system identifies up to 25% of successfully processed slides as requiring no further review and also identifies at least 15% of all successfully processed slides for a second manual review.

The current supplement was submitted to modify the indication for the AutoPap® Primary Screening System which is now called the BD FocalPoint™ GS Imaging System.

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II. INDICATIONS FOR USE

A. Intended Use

The BD FocalPoint™ GS Imaging System is intended to assist in cervical cancer screening of BD SurePath™ Pap Test slides to detect evidence of squamous carcinoma, adenocarcinoma and their usual precursor conditions. These slides will be ranked according to the likelihood of abnormality, and provide relocation and visual review of up to 10 fields of view (FOVs) most likely to contain abnormal cells. Additionally, the system identifies at least 15% of all successfully processed slides with the BD FocalPoint™ Slide Profiler* Directed QC Technology™ for a directed QC re-screen.

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

III. CONTRAINDICATIONS

There are no known contraindications for use.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the BD FocalPoint™ GS Imaging System labeling (Attachment 1).

V. DEVICE DESCRIPTION

The BD FocalPoint™ GS Imaging System includes the (1) BD FocalPoint™ Slide Profiler and the (2) BD FocalPoint™ GS Review Station.

The BD FocalPoint™ Slide Profiler is an automated cytology screening device that classifies slides using a high speed video equipped microscope and image interpretation software to image and analyze the complex images on a cervical cytology slide. With over 100 object features, the FocalPoint Slide Profiler algorithm produces a slide score (probability of abnormality) for every Pap slide and sorts and ranks the slides based on their scores.

Previously, for each FocalPoint instrument, a primary threshold in the score values is established. The slides with scores below the primary threshold, but not more than 25% of all successfully processed slides are classified as *No Further Review* (NFR) and these slides are archived as NILM. However when the FocalPoint Slide Profiler is combined with Focal Point GS Review Station as in

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this application (BD FocalPoint™ GS Imaging System), the “No Further Review” option is disabled and all slides must be subjected to review. The remaining slides (at least 75%) are classified as Further Review slides. The Further Review slides scores are divided into five equal quintiles. The first quintile (slides with highest scores) is then selected for *Quality Control (QC) Review* (at least 15% of all successfully processed slides).

The BD FocalPoint™ GS Review Station reads SurePath™ Pap Test slide processing data from the BD FocalPoint™ Slide Profiler. These data (slide identification, ranking and specimen quality indicators, associated cell pattern images, slide reference frame data, and processing status for each slide) are presented to a cytotechnologist to assist in interpretation of the specimen. In addition, it identifies up to 11 fields of view (FOV) on a slide, one for ease of location confirmation, and up to 10 that are most likely to contain abnormal cells. The order of fields is by likelihood of containing abnormality.

The cytotechnologists review all FOVs. If all FOVs are normal and the specimen is adequate, then the entire slide is considered normal (NILM). If at least one FOV contains an object of interest (abnormality), then the entire slide is to be reviewed (Full Microscopic Slide Review). The coordinates are retained for future relocation.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

The primary procedure for screening liquid based Pap slides is the cytotechnologist review of the entire slide using manual microscopy. In addition, there is one other similar system with FDA approval for scanning liquid-based Pap slides with automated microscopy.

VII. MARKETING HISTORY

Please note the different device names which refer to different instruments with varying features.

The BD FocalPoint™ Slide Profiler has been marketed in 17 countries: Australia, Belgium, Canada, China, Denmark, Germany, Hong Kong, Ireland, Italy, Japan, New Zealand, South Africa, South Korea, Switzerland, The Netherlands, United Kingdom and United States.

The FocalPoint GS system has been marketed in 13 countries: Australia, Belgium, Denmark, France, Germany, Hong Kong, Italy, New Zealand, South Africa, South Korea, Switzerland, The Netherlands, and the United Kingdom.

Historically Marketed Versions That Are No Longer Commercially Available

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The AutoPap® 300 QC System was marketed and used in the following countries between October 1995 and May 2001: Australia, Austria, Belgium, Denmark, Germany, Hong Kong, Japan, Korea, and the United States.

Neither the BD FocalPoint™ Slide Profiler nor BD FocalPoint™ GS Review Station has been withdrawn from the market in any country.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The BD FocalPoint™ GS Imaging System poses no direct risk and only indirect risk to the patient when used to assist in screening cervical cytology slides. An indirect risk includes a potential false negative result that is associated with the devices' ability to effectively sort and rank Pap test slides and select the 10 fields of view (FOVs) that are most likely to contain cellular abnormalities. If the FOVs most likely to contain abnormality are not selected and displayed for the cytotechnologist, this may result in a false negative diagnosis.

False negative diagnoses result when a slide is interpreted as containing no abnormalities when disease is actually present and may result in delayed diagnosis or treatment for the patient. Another indirect risk may be false positive diagnoses which result when a slide is interpreted as containing abnormalities when 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. FOV Selection Repeatability Study

In 2002, a study was conducted to evaluate the repeatability of the BD FocalPoint™ GS Imaging System FOV Selection process. This study evaluated the likelihood that a FOV that had been selected for GS Review would be selected again in a second slide processing run.

Study Design

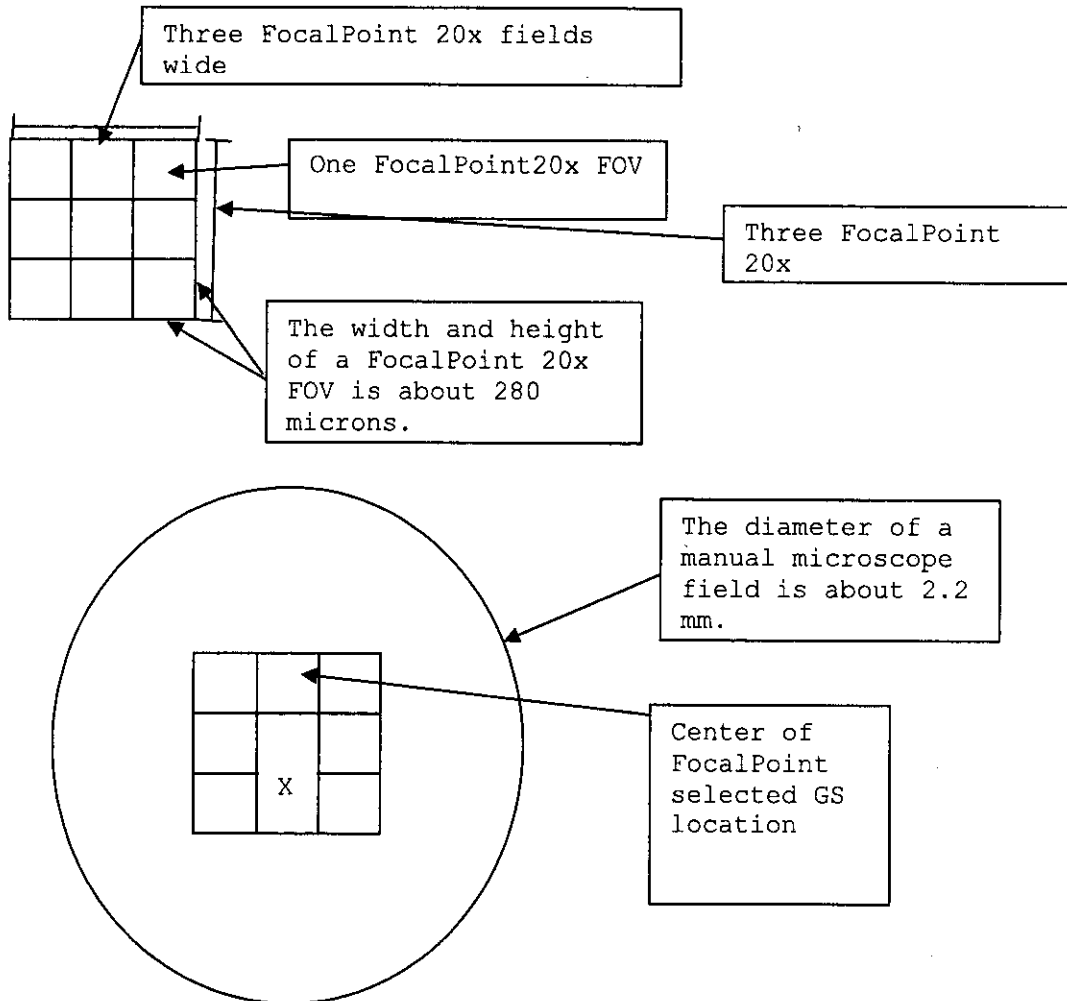
One set of 250 negative (with endocervical component) SurePath Pap Test slides and a second set of 250 abnormal SurePath Pap Test slides were processed twice on a BD FocalPoint™ Slide Profiler running APPS 3.0.0 software. Data obtained from slides successfully processed during both runs were used for the evaluation.

For each slide and processing run, up to 10 FOVs with the highest probability of abnormality were ranked and locations determined. The FOV locations from the two runs were compared. FOV locations are selected by the BD FocalPoint™ GS Imaging System based upon the cell contents of a 3x3 region of 20x FOVs. The width and height of a 20x FOV is approximately 280 µm. If the distance between the center of a selected FOV location from one run and the center of a selected FOV location from the second run was smaller than three times the BD

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FocalPoint™ Slide Profiler 20x FOV size or approximately 840 μm (a conservative range representing a 10x manual microscope field of about 2.2 mm), then the locations were considered repeatedly selected.

GS locations are selected by the FocalPoint based upon the cell contents of a 3x3 region of FocalPoint 20x FOVs.



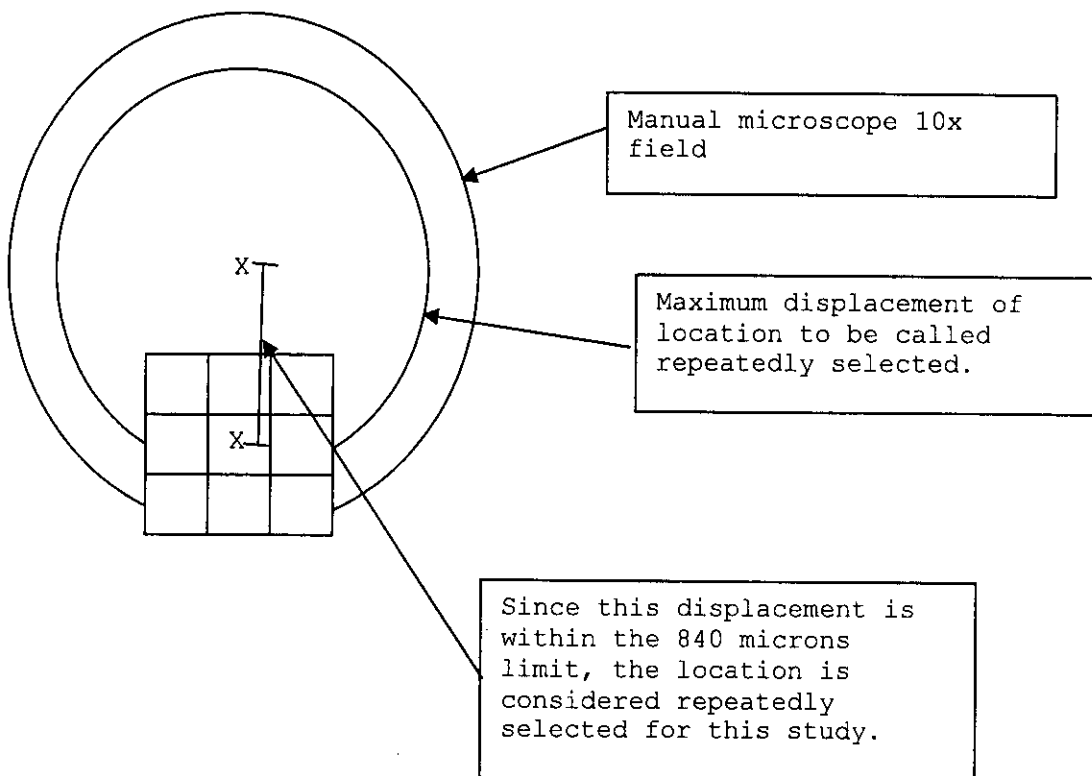
For this study, if the center of the selected GS locations were within 3 FocalPoint 20x field widths ($280 * 3 \Rightarrow 840\text{microns}$), then the location was said to have been repeatedly selected.



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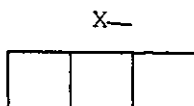
Manual microscope
10x field

Example of a repeatedly selected field.



Results

Two hundred and forty four (244) negative slides and 236 abnormal slides were successfully processed during both runs, with 10 FOVs selected for each run. For each slide and processing run, the set of 10 FOVs were ranked from one (highest likelihood of abnormality) to 10 (lower likelihood). For each slide, the locations and ranks of the two sets of 10 FOVs were compared. The results were averaged over the negative and abnormal slide sets to determine probabilities of re-



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selection. See Figures 1 and 2 below. The average probability of re-selecting rank 1 through rank 10 locations was 45.1% for the negative slide set, and 53.0% for the abnormal slide set. This compares to an approximate 20% random re-selection probability calculated as the area ratio of 10x fields versus the entire nominal SurePath Pap Test specimen area.

Figure 1 – Probability of Re-Selection of Rank 1 through Rank 10 Locations - Negative Slide Set

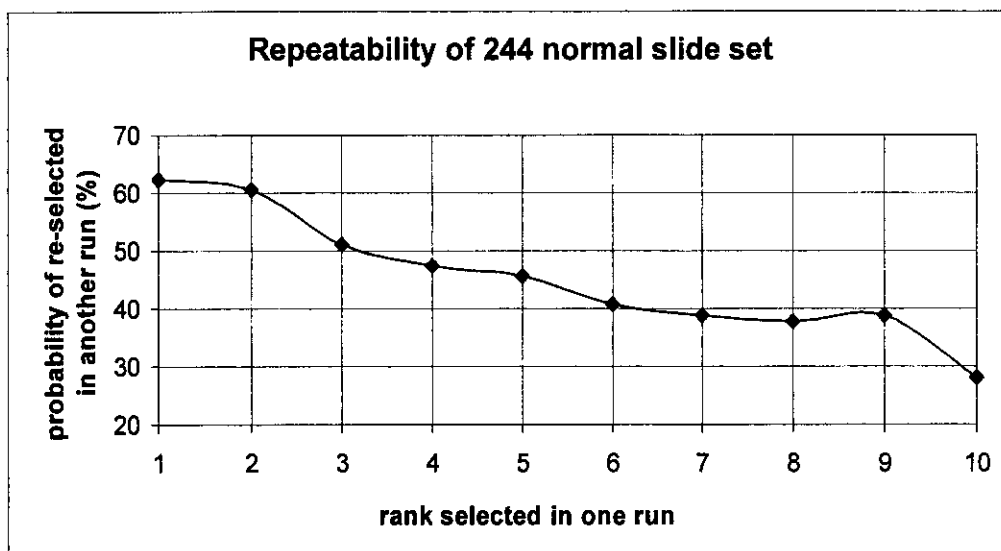
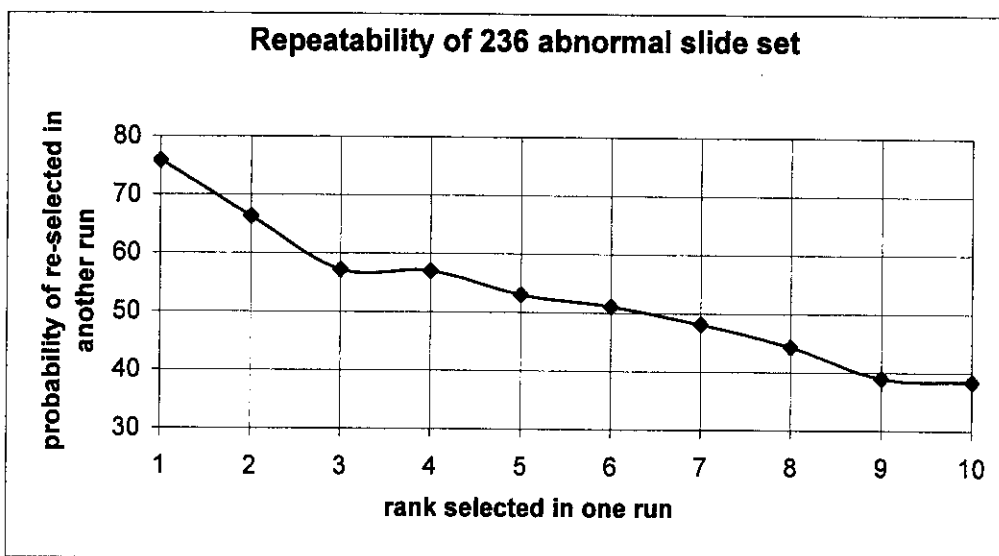


Figure 2 – Probability of Re-Selection of Rank 1 through Rank 10 Locations - Abnormal Slide Set

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Conclusions

For both negative and abnormal slide sets, the probability of re-selecting FOV locations generally decreases as rank increases. The limited sample size may account for the slightly higher rank 9 bump observed for the negative slide set.

Prior investigation has shown that the FOV scores from locations identifying abnormal cells are significantly higher than FOV scores from locations identifying only normal cells. Therefore, the probability of switching ranks between locations with abnormality and locations with normal cells would be expected to be lower than the probability of switching ranks among the locations with only normal cells. The probabilities for each rank reported for negative and abnormal slides given in Figures 1 and 2 show a similar trend.

B. Thin Layer Endocervical Score Study

In 2002, a study was conducted to estimate the effectiveness of the newly designed endocervical score for SurePath Pap Test slides (SurePath Endocervical Score).

Study Design

Three thousand one hundred and eighty six (3,186) negative SurePath Pap Test slides (1,297 with endocervical component, and 1,889 without endocervical component) were used to estimate endocervical scoring effectiveness. These slides came from five sources purposefully chosen to ensure a variety of stain and preparation characteristics. The slides were run on three BD FocalPoint™ Slide Profilers. It is only the BD FocalPoint™ Slide Profiler component of the BD FocalPoint™ GS Imaging system that is utilized for endocervical component detection. Slides were run multiple times to allow averaging of results and analysis of variation. Data from a total of 9,711 slide runs were collected and analyzed.

Each of the slide sets from the five sources was evaluated for compatibility with

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the BD FocalPoint™ Slide Profiler using established criteria. One slide set did not pass all compatibility criteria but was used in the data analysis to ensure characterization of performance across a broad range of specimen preparation characteristics.

As the slides used in this study were also used to design the same SurePath Endocervical Score that was being evaluated, a direct, independent measurement of score performance was not possible. Therefore, a measurement methodology to minimize re-substitution bias was used. SurePath Endocervical Score performance was estimated using cross-validation. The data from the slides in this study were broken into six subsets. Six score classifiers were developed following the same development process as used for the SurePath Endocervical Score. Each of the six score classifiers was developed with a unique data set. The six unique data sets were the combination of five of the six subsets; a different one of the data subsets was withdrawn from the whole, or “held out” for each of the six unique data sets. After each score classifier was developed, performance results were estimated using the data subset that had been held out. Results from all six tests were collated to provide an overall estimate of performance of the SurePath Endocervical Score.

The data from each slide source were evaluated separately to look for lab-to-lab SurePath Endocervical Score performance variations.

Data from each BD FocalPoint™ Slide Profiler was evaluated separately to investigate instrument induced variations in SurePath Endocervical Score performance.

Finally, data from slides designated by the BD FocalPoint™ Slide Profiler as “No Further Review” and “Review” were evaluated separately to investigate any possible differences in SurePath Endocervical Score performance between the two slide populations.

Results

1. When compared to the prior endocervical score, the estimated performance of the SurePath Endocervical Score was significantly better.
2. Difference in performance of the SurePath Endocervical Score was noted for slides where a conventional and SurePath Pap Test slide were made from a single sample compared to SurePath Pap test samples. The source of the difference was traced to the reduced cellularity of slides that were created during a prior clinical trial. These “clinical trial slides” were created as part of a process where two slides were made from a single sampling; a conventional slide was created first and then the cells remaining on the sampling device were preserved for use in making a SurePath Pap Test slide.
3. No variation in SurePath Endocervical Score performance was noted from BD FocalPoint™ Slide Profiler instrument to instrument.

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4. Difference in performance of the SurePath Endocervical Score was observed when comparing performance for Review slides with that for No Further Review. SurePath Endocervical Score performance was better for the No Further Review set. The study conclusion was that this performance difference was due to significantly fewer artifact objects being on No Further Review slides when compared to Review slides.

The positive predictive value of the SurePath Endocervical Score was estimated to be improved when compared to that for the prior endocervical score.

C. Electrical Safety and Electromagnetic Compatibility Testing

The BD FocalPoint™ Slide Profiler was tested and determined to meet the applicable requirements of the following electrical safety and EMC standards:

1. UL 3101-1, 1st Ed. – Electrical Equipment for Laboratory Use
2. CAN/CSA C22.2 No. 1010.1-92 – Safety Requirements for Electrical Equipment for Measurement, Control and Laboratory Use
3. IEC 1010-1 & EN 61010-1:1993 – Safety Requirements for Electrical Equipment for Measurement, Control and Laboratory Use – Part 1: General Requirements
4. EN 60601-1-2:2001 – Medical Electrical Equipment – Part 1-2: General Requirements for Safety – Collateral Standard: Electromagnetic Compatibility – Requirements and Tests

The BD FocalPoint™ GS Review Station was tested and determined to meet the applicable requirements of the following electrical safety and EMC standards:

1. UL 3101-1, 1st Ed. – Electrical Equipment for Laboratory Use
2. CAN/CSA C22.2 No. 1010.1-92 – Safety Requirements for Electrical Equipment for Measurement, Control and Laboratory Use
3. EN 61010-1:1993 – Safety Requirements for Electrical Equipment for Measurement, Control and Laboratory Use – Part 1: General Requirements
4. EN 61326:1997 – Electrical Equipment for Measurement, Control and Laboratory Use – EMC Requirements

X. SUMMARY OF CLINICAL STUDIES

A. Study Design

A multicenter, prospective, two-armed clinical study was designed to evaluate the effectiveness of the BD FocalPoint™ GS Imaging System in the screening of BD SurePath™ Pap Test slides prepared by the BD PrepStain™ System. This study was conducted at four CLIA-certified clinical lab sites in the United States from July 2006 through January 2007, evaluating 12,732 slides with a minimum of 2,500 slides per site. An additional independent institution was used as the adjudication center. The results of the BD FocalPoint™ GS Imaging Systems'

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interpretations were compared with the results of the clinical sites' Current Practice (Manual Screening) study arm, and both arms were compared with "cytology truth" as determined by the Cytology Adjudication Center or (CAC).

In addition to the sites' prospective slides, a total of 422 slides from Sponsor-provided BD SurePath™ Pap Test samples from subjects with a history of cervical cancer and slides prepared at each site from appropriately stored BD SurePath™ pellets collected from subjects whose Pap results were determined to be abnormal were randomly seeded.

Seeded slides were processed through both study arms and screened by the same group of cytotechnologists that screened the slides being reviewed for clinical purposes. Cytotechnologists were blinded to the slide seeding processes.

For the control arm of the study (manual screening), the protocol required the slides to be processed per routine practice, and the final diagnosis made by the laboratory was entered into the Case Report Forms (CRFs). The same slides were then entered into the experimental BD FocalPoint™ GS Imaging System arm of the study. The seeded slides were not archived slides entered into the study but rather slides prepared at the same time as the clinical samples from either BD SurePath™ Pap Test residual pellets that were from cytology samples that were previously diagnosed as abnormal at the same site (422 samples) and stored according to the product insert, or they were from BD SurePath™ Pap Test collection vials supplied by TriPath (62 samples). These seeded samples were processed with fabricated clinical information so as to 'blind' the Investigational Site cytotechnologists and pathologists from identifying the seeded samples as study samples. The study was a prospective study design such that the previous diagnoses on the seeded samples were not used and the control arm diagnosis was that of a new processed slide evaluated without the knowledge of the previous processing and diagnosis taken from the material of the BD SurePath™ Pap Test residual pellet.

This study was conducted at clinical cytology laboratories whose personnel were trained to screen and evaluate BD SurePath™ Pap Test cervical cytology specimens. The study design included two study arms:

1. Manual Initial Screening (Control Arm)

The laboratory's current practice, which consisted of:

- a. 100% manual initial screening,
- b. At least 10% random re-screening (designated as quality control or QC)
- c. Handling of slides according to current laboratory policy for hierarchical review and directed QC. All normal quality control policies were applied.

2. BD FocalPoint™ GS Imaging System (Investigational Arm)

The investigational arm, which consisted of:

- a. 100% BD FocalPoint™ Slide Profiler primary screening,

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- b. Review of identified FOVs on the GS Review Station as a screening tool,
- c. Handling of slides according to current laboratory policy for hierarchical review and directed QC. All quality control policies that applied to the control arm were also applied without deviation to the BD FocalPoint™ GS Imaging System arm.

All BD SurePath™ Pap Test samples had slides prepared using the BD PrepStain™ System. As a general guideline, subjects whose slides had an additional QC rescreen performed had prior history of additional caution in screening. Therefore, all slides that met the criteria in the Control arm of the study were also screened under the same procedures in the investigational BD FocalPoint™ GS Imaging System arm of the study. Finally, there were no restrictions based on previous patient history in the slide types utilized in this study.

B. Study Population

A total of 12,732 BD SurePath™ Pap Test slides were assigned study ID numbers. The slides came from three sources at the four enrolling sites:

- a. 12,310 prospectively prepared slides generated from the BD SurePath™ Pap Test collection vials meeting study inclusion criteria that were presented to one of the four sites for routine Pap testing;
- b. 360 slides prospectively prepared from appropriately stored BD SurePath™ Pap Test pellets from previously collected BD SurePath™ Pap Test abnormal samples, which were reprocessed at the time of the study, and seeded randomly into the routine clinical workload;
- c. 62 prospectively prepared slides from sponsor-provided BD SurePath™ Pap Test cervical specimens collected from subjects previously diagnosed with cervical cancer.

1. Inclusion Criteria

Slides included in the study population met the following criteria:

- a. BD SurePath™ Pap Test slides, prepared using the PrepStain System.
- b. BD SurePath™ Pap Test slides collected from women aged 18-75.
- c. BD SurePath™ Pap Test slides suitable for BD FocalPoint™ Slide Profiler processing.
- d. BD SurePath™ Pap Test slides with markings (such as, ink dots, or hand written markings) on the slide, coverslip, or barcode label that can be removed according to standard laboratory procedures.

2. Exclusion Criteria

Slides were excluded from the study if they were unsuitable for processing or inappropriate for use and didn't meet the criteria listed above. Specimens themselves were excluded depending upon the criteria used in each individual investigational site to determine specimen/paperwork acceptability.

- a. Slide preparations that were not BD SurePath™ Pap Test slides.
- b. Broken or cracked BD SurePath™ Pap Test slides or slide coverslips.
- c. BD SurePath™ Pap Test slides without essential clinical information for diagnosis

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- d. BD SurePath™ Pap Test slides that were part of a multiple-slide case.
- e. Slides that did not meet the inclusion criteria.
- f. BD SurePath™ Pap Test slides that did not successfully process on the BD FocalPoint™ Slide Profiler.
- g. BD SurePath™ Pap Test slides with markings (such as, ink dots, or hand written markings) on the slide, coverslip, or barcode label that could not be removed according to standard procedures.

C. Study Sites

The multi-center trial was conducted at: Boyce and Bynum Pathology Laboratory, Columbia, MO, (Cynthia Kemper, CT, Principal Investigator); Cyto Laboratories, San Antonio, TX, (Thomas J. Molina, M.D., Ph.D., Principal Investigator); Massachusetts General Hospital, Boston, MA, (David C. Wilbur, M.D., Principal Investigator); and Quest Diagnostics, Schaumburg, IL, (Kurian P. Abraham, M.D., Principal Investigator).

D. Site Characteristics

The four geographically diverse clinical trial sites were all previous BD SurePath™ Pap Test laboratories. The characteristics of the study sites are summarized in Table 3.

Table 3 - Site Characteristics

Site	1	2	3	4
Study ASC-US+ prevalence	2.4%	4.5%	3.2%	4.5%
Study HSIL+ prevalence	0.3%	0.9%	0.3%	0.9%
BD SurePath™ Pap Tests Per Year	48,000	122,000	38,500	35,000
Number of Cytotechnologists in Study	4	4	4	4
Number of Cytopathologists in Study	2	2	2	3

Table 4 demonstrates study site prevalence rates with seeded samples included.

Table 4 - Characteristics of the Clinical Study Sites (Seeded Samples Included)

Site	1	2	3	4
Study ASC-US+ prevalence*	9.0%	11.9%	8.1%	12.8%
Study HSIL+ prevalence*	1.2%	2.1%	1.2%	2.0%

*includes seeded samples

E. Slide Accountability

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Table 5 – Distribution of Study Slides by Site

Site	Prospective	Seeded	Total Slides
10	2,667	125	2,792
20	3,339	178	3,517
30	2,937	75	3,012
40	3,367	44	3,411
Total	12,310	422	12,732

Of the 12,732 slides originally assigned study slide ID numbers, 345 (2.7%) were excluded. These exclusions were fairly well distributed among the enrolling sites as shown in Table 5.

Screening failures that were not detected until after the study slide ID number had been assigned were categorized in the slide enrollment log as being “Not Enrolled”. These 71 (0.6%) slides were not processed through the BD FocalPoint™ Slide Profiler. They are also detailed in the Table 6.

Table 6 – Distribution of Excluded Slides by Category/Site

Site	Excluded Slides	“Not Enrolled” Slides	Total Exclusions
10	70	27	97
20	89	4	93
30	101	17	118
40	85	23	108
Total	345	71	416

Once excluded slides were removed from the pool of slides, the total evaluable slides for this intended use trial numbered 12,316. After completion of the study, three additional slides, (one from site 20 and two from site 40), were excluded due to incomplete data. This relates to a total of 419 slides excluded from the study prior to statistical analysis. A total 12,313 slide results were submitted for statistical analysis.

F. Specimen Adequacy

The BD FocalPoint™ Slide Profiler provided information to cytotechnologists on certain characteristics of slide adequacy for all successfully processed slides. For each slide with adequate cellularity, the BD FocalPoint™ Slide Profiler provided the following: (1) presence/absence of squamous component; (2) presence/absence endocervical component. The study used the following information below for determination of slide adequacy:

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TBS 2001

According to TBS 2001, a slide is “*Satisfactory for evaluation*” if the following criteria apply:

- i. An estimated minimum of at least 5,000 well-visualized / well-preserved squamous cells are present
- ii. Endocervical component is present or absent
- iii. Quality Indicator mentioned if 50% - 75% of the cellular components are obscured by inflammation, blood, bacteria, mucus, or artifact that precludes cytologic interpretation of the slide

A slide is classified as “*Unsatisfactory for evaluation*” by TBS 2001 if any of the following apply:

- i. An estimated minimum of less than 5,000 well-visualized / well-preserved squamous cells are present determined by cell counts performed on representative fields
- ii. 75% or more of the cellular components are obscured by inflammation, blood, bacteria, mucus, or artifact that precludes cytologic interpretation of the slide
- iii. Specimen rejected/not processed (specify reason)
- iv. Specimen processed and examined, but unsatisfactory for evaluation of epithelial abnormality because of (specify reason)

Those slides that were determined to be abnormal or “Unsatisfactory” but had not previously gone to the CAC were forwarded to the CAC for “cytology truth” determination.

G. Endocervical Cell Component Results

A revised endocervical cell (EC) component detection algorithm was implemented to improve the BD FocalPoint™ GS Imaging System indication for the presence or absence of EC. Both this revised EC detection algorithm and the previously implemented EC detection algorithm evaluated slides in this study.

Results from these two algorithms were collated to determine the predictive value of the BD FocalPoint™ GS Imaging System’s designation of EC Sufficient/Insufficient. Truth regarding the EC status of cases is derived from the CAC ‘cytology truth’ designation for each case. One thousand nine hundred fifty-seven (1,957) slides were designated Negative (NILM) by CAC. Since no discrepancy resolution occurred for adequacy related information at CAC, only data for 1,613 NILM slides with concurrent EC results are presented below. Tables 7 and 8 give the results for the Prior and Revised EC detection algorithms for CAC designated Negative (NILM) non-atrophic slides.

Table 7 – NILM Slides Containing EC (CAC Designation)

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		Prior EC Detection Algorithm		Total
		Insufficient	Sufficient	
Revised EC Detection Algorithm	Insufficient	76	126	202
	Sufficient	363	935	1,298
Total		439	1,061	1,500

Among 1,500 NILM slides designated by CAC as “Sufficient”, Revised and Prior EC algorithms detected as “Sufficient” 86.5% (1298/1500) and 70.7% (1061/1500) slides correspondingly. Improvement was 15.8% with 95% CI: 13.0% to 18.6%.

Table 8 – NILM Slides Not Containing EC (CAC Designation)

		Prior EC Detection Algorithm		Total
		Insufficient	Sufficient	
Revised EC Detection Algorithm	Insufficient	16	38	54
	Sufficient	12	47	59
Total		28	85	113

Among 113 NILM slides designated by CAC as “Insufficient”, Revised and Prior EC algorithms detected as “Insufficient” 47.8% (54/113) and 24.8% (28/113) slides correspondingly. Improvement was 23.0% with 95% CI: 11.1% to 34.0%.

Table 9 provides the predictive values for the Prior and Revised EC detection algorithms. Slides with discrepancy between experts in CAC were not included in this calculation. The comparison of prior and revised EC detection algorithms was not established for all NILM slides.

Table 9 – Predictive Values – EC Detection Algorithms

	Positive Predictive Value (Positive – Contains EC)	Negative Predictive Value (Negative – Does not contain EC)
Prior EC Detection Algorithm	92.6% (1,061/1,146)	6.0% (28/467)
Revised EC Detection Algorithm	95.7% (1,298/1,357)	21.1% (54/256)

H. BD FocalPoint™ Slide Profiler Quintile Ranking

For every slide that the BD FocalPoint™ Slide Profiler determines to have sufficient cellularity, the BD FocalPoint™ Slide Profiler provides a quintile rank that corresponds to the slide’s likelihood of containing abnormality. The quintile rank is expressed as a number from 1 to 5, where quintile 1 indicates that the slide

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is in the set of slides most likely (top 20%) to contain abnormality. Table 10 shows the number of abnormal slides as determined by the CAC (cytology truth adjudication) panel with their associated quintile rank. The adjudicated Negative slides (not shown) were distributed in all five quintiles proportionately.

These data demonstrate that a high proportion of abnormal slides are ranked in quintile 1 and that progressively fewer slides containing abnormality are in the lower likelihood quintiles. Thus, the BD FocalPoint™ Slide Profiler ranking is an effective indicator of likelihood of abnormality.

Table 10 – Abnormal Slides by Rank

		ASC-US	ASC-H	AGC*	LSIL	HSIL**	Squamous Cancer	Adeno Cancer	Total
Quintile	1	175	17	4	343	130	26	5	700
	2	121	7	0	116	10	5	0	259
	3	89	1	2	55	7	0	0	154
	4	61	0	1	27	1	0	1	91
	5	43	0	1	26	1	0	0	71
	5***	7	1	0	8	6	11	1	34
	Total	496	26	8	575	155	42	7	1,309

* Two of these cases also are ASC-US, one other case is AGC favor neoplasia

** One of these cases also is AGC

*** Slides designated as “Insufficient Squamous” by the BD FocalPoint™ Slide Profiler

In the study there were 12 samples of carcinoma that were found by the device to be limited in squamous cellularity that by convention were ranked as quintile 5 with an accompanying designation that they were “Insufficient Squamous”, or low squamous cellularity cases. Slides were designated as low squamous cellularity because the BD FocalPoint™ Slide Profiler could not locate a sufficient number of squamous epithelial cells. Pap test samples of malignant lesions, including conventional and liquid-based samples, are at significant risk for presenting with low squamous cellularity and concurrent low numbers of malignant cells (Parker, Foti, and Wilbur¹, 2004; Clark and Dawson², 2002; DeMay³, 2005). In premenopausal patients, the low squamous cellularity and rarity of malignant cells are often attributed to excessive blood, inflammation, and necrotic debris associated with the invasive tumor. The latter elements may form the dominant components of the sample, hence diluting the number of malignant cells in the final preparation. In postmenopausal patients, squamous cellularity is often limited as a result of poor sample collection from atrophic epithelium. Regardless of the etiology, samples of low or inadequate squamous cellularity must be considered at increased risk for harboring a significant lesion, and thus deserve additional attention during the screening process. In cases with low squamous cellularity, the BD FocalPoint™ Slide Profiler may not provide FOVs for review at the BD FocalPoint™ GS Review Station resulting in triage to a manual full slide review.

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. Clinical Study Results

1. Determination of Cytology Truth

Slides diagnosed as abnormal or unsatisfactory by either or both study arms were referred to the cytology adjudication center (CAC) for a reference final “cytology truth” diagnosis and adequacy determination (the total number of slides was 1,792). In addition to all abnormal or unsatisfactory slides, at least 10% of the slides from all sites diagnosed as Negative by both study arms (concordant NILMs) were also sent to the CAC for review. The CAC cytopathology panel consisted of six cytopathologists, all Diplomats of the American Board of Pathology in Anatomic and Clinical Pathology, with State of New Jersey licensure. The cytopathologists had between 20 and 32 years of experience.

Each slide was reviewed by two of the six cytopathologists participating on the panel. If the two cytopathologists rendered the same cytology diagnosis, that became the cytology truth. If the two did not render the same diagnosis, a third cytopathologist reviewed the slide. If two out of the three agreed, that diagnosis became cytology truth. If all three rendered different diagnoses, then the three reviewed the slide together under a multi-head microscope and determined the final cytology truth diagnosis.

The CAC results were used as the “Gold Standard” to define the following major “true” categories of the Bethesda System: UNSAT, Negative (or NILM), ASC-US, ASC-H, AGC, LSIL, HSIL, AIS, and Cancer.

Among 12,313 slides, 10,521 slides were diagnosed as Negative by both arms, Manual Screening and BD FocalPoint™ GS Imaging System. Among 10,521 slides with Negative results by both arms, 1,497 (14.2%) random slides were referred to the CAC for truth determination. Among these 1,497 slides, there were 80 (5.34%) slides with a true diagnosis of ASC-US, 4 (0.27%) with a true diagnosis of AGC, and 2 (0.13%) with a true diagnosis of ASC-H. The total number of slides referred to CAC was 3,289 (=1,792 + 1,497).

In this study design (not all slides were referred to the CAC), the ratio of true positive rates of the BD FocalPoint™ GS Imaging System (New test) and Manual Screening (Old test), and the ratio of false positive rates of the BD FocalPoint™ GS Imaging System and Manual Screening can be estimated in an unbiased way⁴. It was demonstrated that the information about the ratio of true positive rates (TPR) and the ratio of false positive rates (FPR) is not sufficient sometimes to draw a conclusion about effectiveness of the New test. If it is anticipated that the performance of the New test is such that increase in FPR is higher than increase in TPR (or samples size is not enough to demonstrate the opposite), estimation of only ratios of TPR and FPR does not allow one to draw conclusions about effectiveness of the New test because information about diagnostic accuracy of the Old test is needed⁵. In this situation, the random sample of the slides diagnosed as Negative by both arms with verified true diagnosis is needed in

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

order to estimate the absolute values of TPR and FPR of the Old test and the New test and then to compare the two tests using the absolute values of true positive rates and false positive rates. For the calculation of absolute difference between sensitivities of the BD FocalPoint™ GS Imaging System and Manual Screening and the calculation of absolute difference between specificities of the BD FocalPoint™ GS Imaging System and Manual Screening along with 95% CI, a multiple imputation technique⁶ was used because the 14.2% of slides with Negative diagnosis by both arms had verification of a true diagnosis by CAC. Because among randomly selected 1,497 slides diagnosed as Negative by both arms, there were 5.34% slides with a true diagnosis of ASC-US, 0.27% slides with a true diagnosis of AGC and 0.13% slides with a true diagnosis of ASC-H; among all 10,521 slides diagnosed as Negative by the both arms, in average, there were 562 “true” ASC-US slides (5.34% x 10,521), 28 “true” AGC slides (0.27% x 10,521) and 14 “true” ASC-H slides (0.13% x 10,521) (where the “true” diagnosis is defined by CAC).

2. Sensitivity and Specificity for the Previously Defined Abnormal Grouping

Tables 11 - 15 compare the ratio of true positive rate (TPR) and ratio of false positive rate (FPR) and difference in sensitivity and specificity results for BD FocalPoint™ GS Imaging System arm versus the Manual Screening arm for slides with a CAC diagnosis of Cancer, HSIL+, LSIL+, ASC-H+ and ASC-US+.

Table 11 – BD FocalPoint™ GS Imaging System vs. Manual Screening results for the slides with CAC determination of Cancer

“Positive” means “Cancer”. Sensitivity is a percent of “true” Cancer slides classified in either study arm as “Cancer” and specificity is a percent of “true” Non-cancer (Combined UNSAT, Neg, ASC-US, ASC-H, AGC, LSIL, HSIL, and AIS) slides classified in either study arm as non-Cancer.

Site	Sensitivity						
	Number of slides Pos by CAC	Number of slides Pos by BD FocalPoint GS	Number of Slides Pos by Manual	Ratio TPR _{GS} /TPR _{Manual}	Sensitivity BD FocalPoint GS	Sensitivity Manual	Difference
1	6	2	1	2.00	33.3%	16.7%	16.7%
2	9	6	5	1.20	66.7%	55.6%	11.1%
3	14	7	5	1.40	50.0%	35.7%	14.3%
4	20	19	11	1.73	95.0%	55.0%	40.0%
All (95% CI)	49	34	22	1.55 (1.12, 2.29)	69.4% (54.6, 81.8)	44.9% (30.7, 59.8)	24.5% (4.8, 42.2)

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

Site	Specificity						
	Number of slides Non-Pos by CAC	Number of slides Non-Pos by BD FocalPoint GS	Number of Slides Non-Pos by Manual	Ratio FPR_{GS}/FPR_{Manual}	Specificity BD FocalPoint GS	Specificity Manual	Difference
1	588	586	586	1.00	99.7%	99.7%	0.0%
2	995	993	995	--	99.8%	100.0%	-0.2%
3	747	747	747	--	100.0%	100.0%	0.0%
4	910	904	909	6.00	99.3%	99.9%	-0.5%
All (95% CI)	3240	3230	3237	3.33 (1.17, 10.00)	99.7% (99.4, 99.9)	99.9% (99.7, 100.0)	-0.2% (-0.5, -0.0)

The results presented in Table 11 show that the BD FocalPoint™ GS Imaging System sensitivity was found to be statistically higher than a manual review by 24.5% for the detection of Cancer. The range of differences in sensitivity was 11.1% to 40.0% among the sites. The Cancer specificity for all sites combined showed a slight decrease for the BD FocalPoint™ GS Imaging System. The range of differences in specificity was -0.5% to 0.0% among the sites.

Table 12 – BD FocalPoint™ GS Imaging System vs. Manual Screening results for the slides with CAC determination of HSIL+

“Positive” means “HSIL+”. Sensitivity is a percent of “true” HSIL+ (combined HSIL, AIS, and Cancer) slides classified in either study arm as “HSIL+” and specificity is a percent of “true” Non-HSIL+ (Combined UNSAT, Neg, ASC-US, ASC-H, AGC, and LSIL) slides classified in either study arm as non-HSIL+.

Site	Sensitivity						
	Number of slides Pos by CAC	Number of slides Pos by BD FocalPoint GS	Number of Slides Pos by Manual	Ratio TPR_{GS}/TPR_{Manual}	Sensitivity BD FocalPoint GS	Sensitivity Manual	Difference
1	32	31	29	1.07	96.9%	90.6%	6.3%
2	72	58	36	1.61	80.6%	50.0%	30.6%
3	35	28	27	1.04	80.0%	77.1%	2.9%
4	65	57	42	1.36	87.7%	64.6%	23.1%
All (95% CI)	204	174	134	1.30 (1.18, 1.43)	85.3% (79.7, 89.9)	65.7% (58.7, 72.2)	19.6% (12.7, 26.8)

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

Site	Specificity						
	Number of slides Non-Pos by CAC	Number of slides Non-Pos by BD FocalPoint GS	Number of Slides Non-Pos by Manual	Ratio FPR_{GS}/FPR_{Manual}	Specificity BD FocalPoint GS	Specificity Manual	Difference
1	562	546	551	1.45	97.2%	98.0%	-0.9%
2	932	879	920	4.42	94.3%	98.7%	-4.4%
3	726	685	691	1.17	94.4%	95.2%	-0.8%
4	865	823	851	3.00	95.1%	98.4%	-3.2%
All (95% CI)	3085	2933	3013	2.11 (1.71, 2.65)	95.1% (94.3, 95.8)	97.7% (97.1, 98.2)	-2.6% (-3.4, -1.9)

The results presented in Table 12 show that the BD FocalPoint™ GS Imaging System sensitivity was found to be statistically higher than a manual review by 19.6% for the detection of HSIL+. The range of differences in sensitivity was 2.9% to 30.6% among the sites. The HSIL+ specificity for all sites combined showed a decrease for the BD FocalPoint™ GS Imaging System. The range of differences in specificity was -4.4% to -0.8% among the sites.

Table 13 – BD FocalPoint™ GS Imaging System vs. Manual Screening results for the slides with CAC determination of LSIL+

“Positive” means “LSIL+”. Sensitivity is a percent of “true” LSIL+ (combined LSIL, HSIL, AIS, and Cancer) slides classified in either study arm as “LSIL+” and specificity is a percent of “true” Non-LSIL+ (Combined UNSAT, Neg, ASC-US, ASC-H and AGC) slides classified in either study arm as non-LSIL+.

Site	Sensitivity						
	Number of slides Pos by CAC	Number of slides Pos by BD FocalPoint GS	Number of Slides Pos by Manual	Ratio TPR_{GS}/TPR_{Manual}	Sensitivity BD FocalPoint GS	Sensitivity Manual	Difference
1	156	133	129	1.03	85.3%	82.7%	2.6%
2	222	197	167	1.18	88.7%	75.2%	13.5%
3	131	126	129	0.98	96.2%	98.5%	-2.3%
4	270	215	170	1.27	79.6%	63.0%	16.7%
All (95% CI)	779	671	595	1.13 (1.09, 1.18)	86.1% (83.5, 88.5)	76.4% (73.2, 79.3)	9.8% (6.7, 12.9)

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

Site	Specificity						
	Number of slides Non-Pos by CAC	Number of slides Non-Pos by BD FocalPoint GS	Number of Slides Non-Pos by Manual	Ratio FPR_{GS}/FPR_{Manual}	Specificity BD FocalPoint GS	Specificity Manual	Difference
1	438	408	413	1.20	93.2%	94.3%	-1.1%
2	782	704	760	3.55	90.0%	97.2%	-7.2%
3	630	539	476	0.59	85.6%	75.6%	10.0%
4	660	575	625	2.43	87.1%	94.7%	-7.6%
All (95% CI)	2510	2226	2274	1.20 (1.05, 1.37)	88.7% (87.4, 89.9)	90.6% (89.4, 91.7)	-1.9% (-3.3, 0.6)

The results presented in Table 13 show that the BD FocalPoint™ GS Imaging System sensitivity was found to be statistically higher than a manual review by 9.8% for the detection of LSIL+. The range of differences in sensitivity was -2.3% to 16.7% among the sites. The LSIL+ specificity for all sites combined was not statistically significantly different between study arms. The range of differences in specificity was -7.6% to 10.0% among the sites.

Table 14 – BD FocalPoint™ GS Imaging System vs. Manual Screening results for the slides with CAC determination of ASC-H+

“Positive” means “ASC-H+”. Sensitivity is a percent of “true” ASC-H+ (combined ASC-H, AGC, LSIL, HSIL, AIS, and Cancer) slides classified in either study arm as “ASC-H+” and specificity is a percent of “true” Non-ASC-H+ (Combined UNSAT, Neg, and ASC-US) slides classified in either study arm as non-ASC-H+.

Site	Sensitivity						
	Number of slides Pos by CAC	Number of slides Pos by BD FocalPoint GS	Number of Slides Pos by Manual	Ratio TPR_{GS}/TPR_{Manual}	Sensitivity BD FocalPoint GS	Sensitivity Manual	Difference
1	160	140	137	1.02	87.5%	85.6%	1.9%
2	237	213	186	1.15	89.9%	78.5%	11.4%
3	137	130	134	0.97	94.9%	97.8%	-2.9%
4	277	224	175	1.28	80.9%	63.2%	17.7%
All (95% CI)	811	707	632	1.12 (1.08, 1.16)	87.2% (84.7, 89.4)	77.9% (74.9, 80.7)	9.2% (6.4, 12.2)

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

Site	Specificity						
	Number of slides Non-Pos by CAC	Number of slides Non-Pos by BD FocalPoint GS	Number of Slides Non-Pos by Manual	Ratio FPR_{GS}/FPR_{Manual}	Specificity BD FocalPoint GS	Specificity Manual	Difference
1	434	400	409	1.36	92.2%	94.2%	-2.1%
2	767	681	737	2.87	88.8%	96.1%	-7.3%
3	624	526	471	0.64	84.3%	75.5%	8.8%
4	653	552	616	2.73	84.5%	94.3%	-9.8%
All (95% CI)	2478	2159	2233	1.30 (1.14, 1.49)	87.1% (85.7, 88.4)	90.1% (88.9, 91.3)	-3.0% (-4.5, -1.5)

The results presented in Table 14 show that the BD FocalPoint™ GS Imaging System sensitivity was found to be statistically higher than a manual review by 9.2% for the detection of ASC-H+. The range of differences in sensitivity was -2.9% to 17.7% among the sites. The ASC-H+ specificity for all sites combined showed a decrease for the BD FocalPoint™ GS Imaging System. The range of differences in specificity was -9.8% to 8.8% among the sites.

Table 15 – BD FocalPoint™ GS Imaging System vs. Manual Screening results for the slides with CAC determination of ASC-US+

“Positive” means “ASC-US+”. Sensitivity is a percent of “true” ASC-US+ (combined ASC-US, ASC-H, AGC, LSIL, HSIL, AIS, and Cancer) slides classified in either study arm as “ASC-US+” and specificity is a percent of “true” Non-ASC-US+ (Combined UNSAT and Neg) slides classified in either study arm as non-ASC-US+.

Site	Sensitivity						
	Number of slides Pos by CAC	Number of slides Pos by BD FocalPoint GS	Number of Slides Pos by Manual	Ratio TPR_{GS}/TPR_{Manual}	Sensitivity BD FocalPoint GS	Sensitivity Manual	Difference
1	242	198	215	0.92	81.8%	88.8%	-7.0%
2	409	328	311	1.06	80.2%	76.0%	4.2%
3	235	198	218	0.91	84.3%	92.8%	-8.5%
4	423	338	337	1.00	79.9%	79.7%	0.2%
All (95% CI)	1309	1062	1081	0.98 (0.95, 1.01)	81.1% (78.9, 83.2)	82.6% (80.4, 84.6)	-1.5% (-4.1, 1.2)

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Site	Specificity						
	Number of slides Non-Pos by CAC	Number of slides Non-Pos by BD FocalPoint GS	Number of Slides Non-Pos by Manual	Ratio FPR_{GS}/FPR_{Manual}	Specificity BD FocalPoint GS	Specificity Manual	Difference
1	352	314	311	0.93	89.2%	88.4%	0.9%
2	595	508	499	0.91	85.4%	83.9%	1.5%
3	526	431	395	0.73	81.9%	75.1%	6.8%
4	507	420	433	1.18	82.8%	85.4%	-2.6%
All (95% CI)	1980	1673	1638	0.90 (0.79, 1.01)	84.5% (82.8, 86.1)	82.7% (81.0, 84.4)	1.8% (-0.3, 3.8)

The results presented in Table 15 show that the ASC-US+ sensitivity for all sites combined was not statistically significantly different between study arms. The range of differences in sensitivity was -8.5% to 4.2% among the sites. The ASC-US+ specificity for all sites combined was not statistically significantly different between study arms. The range of differences in specificity was -2.6% to 6.8% among the sites.

3. Comparisons of Study Arm Diagnoses

Table 16 compares the performance of the Manual Screening arm versus the BD FocalPoint™ GS Imaging System arm for each category of the Bethesda System.

Table 16 – BD FocalPoint™ GS Imaging System Diagnosis vs. Manual Screening Diagnosis

	Manual Screening Diagnosis										
		UNSAT	NEG	ASC-US	ASC-H	AGC	LSIL	HSIL	AIS	CA	Total
BD FocalPoint™ GS Imaging System Diagnosis	UNSAT	16	11	0	0	0	0	0	0	0	27
	NEG	4	10,521	267	8	7	105	4	0	1	10,917
	ASC-US	0	175	123	3	0	39	3	0	0	343
	ASC-H	0	16	12	4	0	4	3	0	0	39
	AGC	0	19	3	1	4	4	1	0	0	32
	LSIL	0	100	121	2	0	379	27	0	0	629
	HSIL	0	26	20	13	1	93	122	0	4	279
	AIS	0	0	0	0	0	0	2	0	1	3
	CA	0	2	0	0	3	1	19	0	19	44
	Total	20	10,870	546	31	15	625	181	0	25	12,313

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

Tables 17 – 23 show the performance of the BD FocalPoint™ GS Imaging System and Manual Screening compared to the final CAC diagnosis for the following categories of the Bethesda System: Cancer, HSIL, LSIL, AGC, ASC-H, ASC-US, and Negative.

Table 17 – BD FocalPoint™ GS Imaging System vs. Manual Screening for Slides Adjudicated as Cancer

	Manual Screening Diagnosis										
		UNSAT	NEG	ASC-US	ASC-H	AGC	LSIL	HSIL	AIS	CA	Total
BD FocalPoint™ GS Imaging System Diagnosis	UNSAT	0	0	0	0	0	0	0	0	0	0
	NEG	0	0	0	0	0	0	0	0	1	1
	ASC-US	0	0	0	0	0	0	0	0	0	0
	ASC-H	0	0	0	0	0	0	0	0	0	0
	AGC	0	0	0	0	0	0	0	0	0	0
	LSIL	0	0	0	0	0	0	0	0	0	0
	HSIL	0	0	0	0	1	0	8	0	3	12
	AIS	0	0	0	0	0	0	1	0	1	2
	CA	0	1	0	0	3	0	13	0	17	34
	Total	0	1	0	0	4	0	22	0	22	49

Among the 49 slides determined Cancer by the CAC, 34 (69.4%) slides in the BD FocalPoint™ GS Imaging System arm and 22 (44.9%) slides in the Manual Screening arm were diagnosed as Cancer. The detection of cancer was numerically higher in the BD FocalPoint™ GS Imaging System arm of the study. Of the 13 cancers undercalled but appropriately triaged by the BD FocalPoint™ GS Imaging System, 12 were classified as HSIL (ASCCP guidelines recommend colposcopy with ECC assessment to manage all women with HSIL⁷) and 1 was classified as a Negative. This “Negative” slide was indicated for a manual full slide review by the BD FocalPoint™ GS Imaging System due to a designation of “Insufficient Squamous” (low squamous cellularity) and subsequently classified as Negative during the cytology review process. In cases with low squamous cellularity, the BD FocalPoint™ Slide Profiler may not provide FOVs for review at the BD FocalPoint™ GS Review Station resulting in triage to a manual full slide review. Of the 27 cancers undercalled by Manual Screening, 22 were classified as HSIL, 4 as AGC, and 1 as Negative.

Table 18 – BD FocalPoint™ GS Imaging System vs. Manual Screening for Slides Adjudicated as HSIL

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

	Manual Screening Diagnosis										
		UNSAT	NEG	ASC-US	ASC-H	AGC	LSIL	HSIL	AIS	CA	Total
BD FocalPoint™ GS Imaging System Diagnosis	UNSAT	0	0	0	0	0	0	0	0	0	0
	NEG	0	0	0	0	0	3	0	0	0	3
	ASC-US	0	0	1	1	0	1	0	0	0	3
	ASC-H	0	0	1	0	0	0	0	0	0	1
	AGC	0	0	0	0	0	0	1	0	0	1
	LSIL	0	0	2	1	0	11	7	0	0	21
	HSIL	0	3	3	7	0	30	72	0	1	116
	AIS	0	0	0	0	0	0	1	0	0	1
	CA	0	0	0	0	0	1	6	0	2	9
	Total	0	3	7	9	0	46	87	0	3	155

Among the 155 slides determined HSIL by the CAC, 116 (74.8%) slides in the BD FocalPoint™ GS Imaging System arm and 87 (56.1%) slides in the Manual Screening arm were diagnosed as HSIL. Three (1.9%) slides in the BD FocalPoint™ GS Imaging System arm and 3 (1.9%) slides in the Manual Screening arm were diagnosed as Negative.

Table 19 – BD FocalPoint™ GS Imaging System vs. Manual Screening for Slides Adjudicated as LSIL

	Manual Screening Diagnosis										
		UNSAT	NEG	ASC-US	ASC-H	AGC	LSIL	HSIL	AIS	CA	Total
BD FocalPoint™ GS Imaging System Diagnosis	UNSAT	0	0	0	0	0	0	0	0	0	0
	NEG	0	0	21	1	0	16	1	0	0	39
	ASC-US	0	11	26	1	0	13	0	0	0	51
	ASC-H	0	0	4	1	0	2	1	0	0	8
	AGC	0	1	0	0	0	0	0	0	0	1
	LSIL	0	22	61	1	0	288	16	0	0	388
	HSIL	0	3	6	1	0	48	30	0	0	88
	AIS	0	0	0	0	0	0	0	0	0	0
	CA	0	0	0	0	0	0	0	0	0	0
	Total	0	37	118	5	0	367	48	0	0	575

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

Among the 575 slides determined LSIL by the CAC, 388 (67.5%) slides in the BD FocalPoint™ GS Imaging System arm and 367 (63.8%) slides in the Manual Screening arm were diagnosed as LSIL. Thirty-nine (6.8%) slides in the BD FocalPoint™ GS Imaging System arm and 37 (6.4%) slides in the Manual Screening arm were diagnosed as Negative.

Table 20 – BD FocalPoint™ GS Imaging System vs. Manual Screening for Slides
Adjudicated as AGC

BD FocalPoint™ GS Imaging System Diagnosis	Manual Screening Diagnosis										
		UNSAT	NEG	ASC- US	ASC- H	AGC	LSIL	HSIL	AIS	CA	Total
	UNSAT	0	0	0	0	0	0	0	0	0	0
	NEG	0	4	0	0	0	0	0	0	0	4
	ASC- US	0	1	0	0	0	0	0	0	0	1
	ASC-H	0	0	0	0	0	0	0	0	0	0
	AGC	0	0	0	0	1	0	0	0	0	1
	LSIL	0	0	0	0	0	0	0	0	0	0
	HSIL	0	0	0	0	0	0	0	0	0	0
	AIS	0	0	0	0	0	0	0	0	0	0
	CA	0	0	0	0	0	0	0	0	0	0
	Total	0	5	0	0	1	0	0	0	0	6

Among the 6 slides determined AGC by the CAC, 1 (16.7%) slide in the BD FocalPoint™ GS Imaging System arm and 1 (16.7%) slide in the Manual Screening arm were diagnosed as AGC. Four (66.7%) slides in the BD FocalPoint™ GS Imaging System arm and 5 (83.3%) slides in the Manual Screening arm were diagnosed as Negative.

Table 21 – BD FocalPoint™ GS Imaging System vs. Manual Screening for Slides
Adjudicated as ASC-H

BD FocalPoint™ GS Imaging System Diagnosis	Manual Screening Diagnosis										
		UNSAT	NEG	ASC- US	ASC- H	AGC	LSIL	HSIL	AIS	CA	Total
	UNSAT	0	0	0	0	0	0	0	0	0	0
	NEG	0	2	0	0	0	0	0	0	0	2
	ASC- US	0	0	0	0	0	0	0	0	0	0
	ASC-H	0	0	0	1	0	1	0	0	0	2
	AGC	0	0	2	1	0	1	0	0	0	4

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

LSIL	0	0	2	0	0	0	2	0	0	4
HSIL	0	0	2	3	0	4	5	0	0	14
AIS	0	0	0	0	0	0	0	0	0	0
CA	0	0	0	0	0	0	0	0	0	0
Total	0	2	6	5	0	6	7	0	0	26

Among the 26 slides determined ASC-H by the CAC, 2 (7.7%) slides in the BD FocalPoint™ GS Imaging System arm and 5 (19.2%) slides in the Manual Screening arm were diagnosed as ASC-H. Two (7.7%) slides in the BD FocalPoint™ GS Imaging System arm and 2 (7.7%) slides in the Manual Screening arm were diagnosed as Negative.

Table 22 – BD FocalPoint™ GS Imaging System vs. Manual Screening for Slides Adjudicated as ASC-US

	Manual Screening Diagnosis										
		UNSAT	NEG	ASC-US	ASC-H	AGC	LSIL	HSIL	AIS	CA	Total
BD FocalPoint™ GS Imaging System Diagnosis	UNSAT	0	0	0	0	0	0	0	0	0	0
	NEG	0	80	79	3	0	36	0	0	0	198
	ASC-US	0	52	47	1	0	15	3	0	0	118
	ASC-H	0	3	5	2	0	0	1	0	0	11
	AGC	0	2	0	0	1	2	0	0	0	5
	LSIL	0	33	36	0	0	63	2	0	0	134
	HSIL	0	10	6	1	0	9	6	0	0	32
	AIS	0	0	0	0	0	0	0	0	0	0
	CA	0	0	0	0	0	0	0	0	0	0
	Total	0	180	173	7	1	125	12	0	0	498

Among the 498 slides determined ASC-US by the CAC, 118 (23.7%) slides in the BD FocalPoint™ GS Imaging System arm and 173 (34.7%) slides in the Manual Screening arm were diagnosed as ASC-US. One hundred ninety-eight (39.8%) slides in the BD FocalPoint™ GS Imaging System arm and 180 (36.1%) slides in the Manual Screening arm were diagnosed as Negative.

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Table 23 – BD FocalPoint™ GS Imaging System vs. Manual Screening for Slides
Adjudicated as Negative

BD FocalPoint™ GS Imaging System Diagnosis	Manual Screening Diagnosis										
		UNSAT	NEG	ASC- US	ASC- H	AGC	LSIL	HSIL	AIS	CA	Total
	UNSAT	1	5	0	0	0	0	0	0	0	6
	NEG	2	1,411	167	4	7	50	3	0	0	1,644
	ASC- US	0	111	49	0	0	10	0	0	0	170
	ASC-H	0	13	2	0	0	1	1	0	0	17
	AGC	0	16	1	0	2	1	0	0	0	20
	LSIL	0	45	20	0	0	17	0	0	0	82
	HSIL	0	10	3	1	0	2	1	0	0	17
	AIS	0	0	0	0	0	0	0	0	0	0
	CA	0	1	0	0	0	0	0	0	0	1
	Total	3	1,612	242	5	9	81	5	0	0	1,957

Among the 1,957 slides determined Negative by the CAC, 1,644 (84.0%) slides in the BD FocalPoint™ GS Imaging System arm and 1,612 (82.4%) slides in the Manual Screening arm were diagnosed as Negative.

4. ASC/SIL Ratios from Manual Screening versus BD FocalPoint™ GS Imaging System

Table 24 displays the ASC/SIL ratios for the Manual Screening arm and the BD FocalPoint™ GS Imaging System arm. ASC is the sum of all ASC-US and ASC-H slides. SIL is the sum of all LSIL, HSIL and Cancer slides. The ASC/SIL ratio includes true positive and false positive slides (as compared to CAC); therefore, Tables 9- 13 provide more detailed information about the ratio of true positive rate and ratio of false positive rate separately.

Table 24 – ASC/SIL Ratios by Study Arm

Site	Manual Screening Arm			BD FocalPoint™ GS Imaging System Arm		
	ASC	SIL	ASC/SIL Ratio	ASC	SIL	ASC/SIL Ratio
1	102	155	0.66	72	163	0.44
2	216	194	1.11	123	274	0.45
3	68	294	0.23	73	215	0.34
4	203	211	0.96	114	300	0.38
All	589	854	0.69	382	952	0.40

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The data in Table 24 indicate that the overall ASC/SIL ratio decreased 42% ((0.69-0.40/0.69)) in the BD FocalPoint™ GS Imaging System arm of the study compared with the Manual Screening arm of the study. This result indicates that the ASC/SIL ratio for the BD FocalPoint™ GS Imaging System is substantially lower than the ASC/SIL ratio of Manual Screening.

5. Unsatisfactory Slides Analysis

Table 25 displays the distribution of the 23 slides determined by the CAC truth determination process to be Unsatisfactory.

Table 25 – Classification of Unsatisfactory Slides (No Adjustment)

		Manual Screening		Total
		Unsat(+)	Sat(-)	
BD FocalPoint ™ GS Imaging System	Unsat (+)	15	6	21
	Sat (-)	2	0	2
	Total	17	6	23

The adjudicated percentage of unsatisfactory slides is 0.70% (23/3285) with exact 95% confidence interval (0.44%, 1.05%). The BD FocalPoint™ GS Imaging System arm correctly assessed the unsatisfactory status of slides 91.3% (21/23) of the time whereas the Manual Screening arm correctly assessed the slide as being unsatisfactory 73.9% (17/23) of the time. This resulted in a 17.4% increase in slides correctly assessed for unsatisfactory status by the BD FocalPoint™ GS Imaging System arm versus the Manual Screening arm. The increase of 17.4% was not statistically significant (95% CI: -8.3% to 42.4%).

6. Benign Cellular Changes for the Manual Screening and BD FocalPoint™ GS Imaging System Arms

Table 26 – Summary of NILM (Negative) or Benign Cellular Changes for the Manual Screening Arm and BD FocalPoint™ GS Imaging System Arms

Site	Any Organism		Reactive Cellular Changes		Atrophy	
	Manual Screening	BD FocalPoint GS	Manual Screening	BD FocalPoint GS	Manual Screening	BD FocalPoint GS
1	154	124	110	70	132	122
2	351	359	9	8	13	27
3	382	391	276	281	241	254
4	523	514	1	8	1	25
All	1,410	1,388	396	367	387	428

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7. Specimen Adequacy for the Manual Screening and BD FocalPoint™ GS Imaging System Arms

Table 27 – Summary of Specimen Adequacy for the Manual Screening Arm and BD FocalPoint™ GS Imaging System Arms

Site	Absence of endocervical component		50%-75% of squamous epithelial cells obscured		Scant cellularity	
	Manual Screening	BD FocalPoint GS	Manual Screening	BD FocalPoint GS	Manual Screening	BD FocalPoint GS
1	220	262	3	1	9	12
2	288	437	46	55	0	2
3	347	434	0	0	12	10
4	135	112	66	8	0	1
All	990	1,245	115	64	21	25

Site	Too few epithelial cells present (less than 5000)		More than 75% of the squamous epithelial cells obscured		Unsatisfactory slide	
	Manual Screening	BD FocalPoint GS	Manual Screening	BD FocalPoint GS	Manual Screening	BD FocalPoint GS
1	9	9	0	0	9	9
2	2	3	2	2	6	11
3	0	3	0	0	1	3
4	6	9	1	0	7	8
All	17	24	3	2	23	31

J. Cytotechnologist Productivity Study/Workload Study

Daily Cytotechnologist Screening Rates

A workload study documenting cytotechnologist screening rates was conducted throughout the course of the BD FocalPoint™ GS Imaging System clinical trial. Workload data collection was similar for both arms and included time spent reviewing clinical information and reporting diagnostic interpretations. The clinical information available to the study participant was similar in both arms. The work environment was the same in both study arms. In the BD FocalPoint™ GS Imaging System workload study arm, five cytotechnologists worked an average of three to four hours, seven cytotechnologists worked an average of four to five hours, and none worked more than an average of five hours. See Table 26.

Four cytotechnologists at each of four sites for a total 16 cytotechnologists participated in the workload evaluation study. Pap test screening experience ranged from two to 36 years. Cytotechnologists who participated in the Manual Screening arm participated in the BD FocalPoint™ GS Imaging System arm but

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did not review the same slides from one arm to the next. Table 28 below provides the workload statistics by study site.

Table 28 shows the screening rates achieved with the BD FocalPoint™ GS Imaging System.

Table 28- Cytotechnologist Screening Rates

Site/CT	Review Methods	Total Number of Slides Evaluated	Average Number of Hours Screened Per Day	Extrapolated Daily Rates (8-hour workday)		
				Low Day	Mean Day	High Day
Site 1	MS	3,258	5.15	52.8	78.1	192.0
	GS	2,823	4.51	75.7	123.5	174.0
1003	MS	836	3.88	52.8	91.1	192.0
	GS	747	4.07	88.0	133.3	174.0
1004	MS	993	6.27	62.4	74.7	84.5
	GS	840	4.85	97.5	128.1	150.0
1005	MS	818	5.40	56.0	72.1	88.0
	GS	870	5.00	98.5	131.7	156.8
1006	MS	611	5.53	59.2	68.4	77.8
	GS	366	4.00	75.7	92.6	107.1
Site 2	MS	4,518	4.70	59.1	90.7	130.0
	GS	3,457	3.81	48.0	98.9	123.8
2000	MS	996	4.11	59.1	79.8	93.3
	GS	951	4.00	84.1	100.1	114.0
2001	MS	1,197	5.21	75.1	87.3	94.9
	GS	793	3.76	84.1	98.3	110.0
2002	MS	1,184	3.88	89.2	112.4	130.0
	GS	875	3.70	48.0	98.5	123.8
2003	MS	1,141	5.81	80.0	82.9	88.0
	GS	838	3.77	88.0	98.7	105.8
Site 4	MS	4,011	3.06	44.1	120.6	185.2
	GS	3,353	4.61	98.6	150.9	240.0
4003	MS	439	2.34	44.1	93.7	138.0
	GS	568	4.85	106.7	133.8	158.2
4004	MS	1,312	3.05	72.2	139.0	185.2
	GS	933	4.82	122.1	172.2	198.1
4005	MS	1,275	3.35	96.0	129.0	153.2
	GS	904	4.64	118.1	154.7	179.2
4008	MS	985	3.30	97.9	110.5	126.3
	GS	948	4.32	98.6	142.6	240.0

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Table 29 – Comparison of Prevalence and Screening Rates

Site	ASC-US+ n (%)*	ASC-H+ n (%)*	LSIL+ n (%)*	HSIL+ n (%)*	Study Arm	Extrapolated Daily Rates [†] (8-hour workday)		
						Low	Mean	High
All	1309 (10.63)	811 (6.59)	779 (6.33)	204 (1.66)	MS	30.8	98.7	212.6
					GS	48.0	129.3	240.0

* Prevalence rates

[†] These numbers are based on all slides in the study to match the table for sensitivity and specificity

Table 30 – Summary of Comparison of BD FocalPoint GS Imaging System and Manual Screening Performances

Site	Study Arm	Performance for ASC-US+ % Difference				Performance for ASC-H+ % Difference				Performance for LSIL+ % Difference				Performance for HSIL+ % Difference			
		Sensitivity		Specificity		Sensitivity		Specificity		Sensitivity		Specificity		Sensitivity		Specificity	
All	MS (%)	82.6	-1.5	82.7	+1.8	77.9	+9.2	90.1	-3.0	76.4	+9.8	90.6	-1.9	65.7	+19.6	97.7	-2.6
	GS (%)	81.1		84.5		87.2		87.1		86.1		88.7		85.3		95.1	

Based on these data, the maximum number of slides examined by an individual using the BD FocalPoint™ GS Imaging System should not exceed 170 slides in a 24 hour period. The maximum number of 170 slides is examined in no less than an 8-hour workday.

For less than an 8-hour workday, the following formula must be applied to determine the maximum number of slides to be reviewed during that workday:

$$\frac{\# \text{ hours spent screening BD SurePath slides using the BD FocalPoint GS Imaging System} \times 170}{8}$$

The BD FocalPoint™ GS Imaging System limit of 170 slides in an 8-hour workday per 24 hour period includes the following:

- Review clinical history and BD FocalPoint™ Slide Profiler information,
- Location confirmation of first FOV,
- Screen up to 10 FOVs at the BD FocalPoint™ GS Review Station microscope,
- Full slide review as needed at the BD FocalPoint™ GS Review Station microscope,
- Record results and triage appropriately.

The manual workload limit does not supersede the CLIA requirement of 100 slides in no less than an 8-hour day per 24 hour period. Manual review includes the following types of slides:

- Full slide review at the BD FocalPoint™ GS Review Station microscope,
- Slides reviewed without the BD FocalPoint™ GS Review Station microscope,
- Non-gynecologic slides

When conducting manual review, refer to the CLIA '88 workload requirements to calculate daily workload per 8-hour day per 24 hour period.

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It is the responsibility of the Technical Supervisor to evaluate and set workload limits for individual cytotechnologists based on laboratory clinical performance.

According to CLIA '88, these workload limits should be reassessed every six months.

Since limits beyond 170 slides per 8-hour work day have not been documented to be safe and effective, workload limits should not exceed the maximum limit specified within the product labeling.

X. CONCLUSIONS DRAWN FROM THE STUDY

1. The BD FocalPoint™ GS Imaging System sensitivity was found to be statistically higher than the manual review of BD SurePath™ Pap Test Slides for the detection of Cancer. The Cancer sensitivity for all sites combined was 69.4% for the BD FocalPoint™ GS Imaging System arm versus 44.9% for the Manual Screening arm resulting in a statistically significant increase of 24.5% with 95% CI: 4.8% to 42.2%. The Cancer specificity for all sites combined was 99.7% for the BD FocalPoint™ GS Imaging System arm versus 99.9% for the Manual Screening arm resulting in a slight decrease of 0.2% with 95% CI: -0.5 to -0.0%.
2. The BD FocalPoint™ GS Imaging System sensitivity was found to be statistically higher than the manual review of BD SurePath™ Pap Test Slides for the detection of HSIL+. The HSIL+ sensitivity for all sites combined was 85.3% for the BD FocalPoint™ GS Imaging System arm versus 65.7% for the Manual Screening arm resulting in a statistically significant increase of 19.6% with 95% CI: 12.7% to 26.8%. The HSIL+ specificity for all sites combined was 95.1% for the BD FocalPoint™ GS Imaging System arm versus 97.7% for the Manual Screening arm resulting in a decrease of 2.6% with 95% CI: -3.4% to -1.9%.
3. The BD FocalPoint™ GS Imaging System sensitivity was found to be statistically higher than the manual review of BD SurePath™ Pap Test Slides for the detection of LSIL+. The LSIL+ sensitivity for all sites combined was 86.1% for the BD FocalPoint™ GS Imaging System arm versus 76.4% for the Manual Screening arm resulting in a statistically significant increase of 9.8% with 95% CI: 6.7% to 12.9%. The LSIL+ specificity for all sites combined was 88.7% for the BD FocalPoint™ GS Imaging System arm versus 90.6% for the Manual Screening arm resulting in a slight decrease of 1.9% (not statistically significant) with 95% CI: -3.3% to 0.6%.
4. The BD FocalPoint™ GS Imaging System sensitivity was found to be statistically higher than the manual review of BD SurePath™ Pap Test Slides

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for the detection of ASC-H+. The ASC-H+ sensitivity for all sites combined was 87.2% for the BD FocalPoint™ GS Imaging System arm versus 77.9% for the Manual Screening arm resulting in a statistically significant increase of 9.2% with 95% CI: 6.4% to 12.2%. The ASC-H+ specificity for all sites combined was 87.1% for the BD FocalPoint™ GS Imaging System arm versus 90.1% for the Manual Screening arm resulting in a decrease of 3.0% with 95% CI: -4.5% to -1.5%.

5. The ASC-US+ sensitivity for all sites combined was 81.1% for the BD FocalPoint™ GS Imaging System arm versus 82.6% for the Manual Screening arm resulting in a slight decrease of 1.5% (not statistically significant) with 95% CI: -4.1% to 1.2%. The ASC-US+ specificity for all sites combined was 84.5% for the BD FocalPoint™ GS Imaging System arm versus 82.7% for the Manual Screening arm were similar (difference was 1.8%; not statistically significant) with 95% CI: -0.3% to 3.8%.
6. Based on results from this study, the maximum daily workload limit when using the BD FocalPoint™ GS Imaging System for primary screening of BD SurePath™ Pap Test slides should not exceed 170 slides per 8-hour workday. This workload limit of 170 slides includes time spent on manual full slide review which should not supersede the CLIA requirement of 100 slides in an 8-hour workday for any type of slide requiring a manual full slide review.
7. For these study sites and these study populations, the data from this clinical trial demonstrate the BD FocalPoint™ GS Imaging System's safe and effective use in the primary screening of BD SurePath™ Pap Test slides in detecting cervical abnormalities for all Bethesda categories. The results of this study support the indication that the sorting and ranking of slides by the BD FocalPoint™ Slide Profiler, in combination with the review of Field of Views (FOVs) at the BD FocalPoint™ GS Review Station, assists in the detection of ASC-US+, in a manner that is at least equivalent to Manual Screening.
8. In the detection of Cancer, HSIL+, LSIL+, and ASC-H+, the BD FocalPoint™ GS Imaging System sensitivity is statistically higher than Manual Screening accompanied by a concurrent increase in Pap test screening productivity.

VALIDATION 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 (result) and a control article (result) was evaluated for each subject.

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 (CRO) to assure adherence to the protocol.

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The statistical methods used to analyze the data were 1) analysis of the correlated proportions; 2) score confidence intervals for the binomial proportions; 3) confidence intervals for the ratio of two correlated proportions; 4) comparison of the two devices in the studies with verification bias; and 5) use of multiple imputation for an adjustment of the verification bias.

The clinical trial data show that for Cancer, the improvement in sensitivity of the BD FocalPoint™ GS Imaging System over the Manual Review method was statistically significant with an increase of 24.5% with a lower limit of 95% confidence interval of 4.8%; for HSIL+, the improvement in sensitivity of the BD FocalPoint™ GS Imaging System over the Manual Review method was statistically significant with an increase of 19.6% with a lower limit of 95% confidence interval of 12.7%; for LSIL+, the improvement in sensitivity of the BD FocalPoint GS Imaging System over the Manual method was statistically significant with an increase of 9.8% with a lower limit of 95% confidence interval of 6.7%; and for ASC-H+, the improvement in sensitivity of the BD FocalPoint™ GS Imaging System over the Manual Review method was statistically significant with an increase of 9.2% with a lower limit of 95% confidence interval of 6.4% for all sites combined. There were either no statistically significant decreases in specificities or decreases in specificities were statistically significant but clinically tolerable.

RISK BENEFIT ANALYSIS

The results of the clinical investigation demonstrated that SurePath™ Pap Test slides reviewed with the BD FocalPoint™ GS Imaging System result in at least equivalent diagnosis for ASC-US+ and statistically higher for detection of Cancer, HSIL+, LSIL+, and ASC-H+ to slides reviewed using the manual method, when used with the 2001 Bethesda System: Terminology for Reporting Results of Cervical Cytology. Use of the device is also accompanied by a concurrent increase in pap test screening rate which do not negatively impact the effectiveness of the BD FocalPoint™ GS Imaging System when screening SurePath™ Pap Test slides.

The BD FocalPoint™ GS Imaging System does not contact the patient and uses slides prepared using the current method for the SurePath™ Pap Test; it has minimal associated physical risks.

Based on the information in the studies provided, FDA has concluded that the benefits of using the BD FocalPoint™ GS Imaging System for its intended use outweighs the risk associated with it.

SAFETY

Based on the valid scientific evidence from the clinical trial, the probable benefits to health from the use of this device for screening cervical specimens outweigh any probable risks. The BD FocalPoint™ GS Imaging System is an in vitro diagnostic test and the instructions for the safe use of this product are included in the package insert.

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EFFECTIVENESS

The data from the clinical study and the supporting cytotechnologist workload study demonstrate that the use of this device to screen for cervical abnormalities is effective and provides a work productivity component as well. Use of the device is also accompanied by a concurrent increase in Pap test screening rate which do not negatively impact the effectiveness of the BD FocalPoint™ GS Imaging System when screening SurePath™ Pap Test slides.

XI. 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, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CDRH DECISION

CDRH issued an approval order on December 3, 2008.

The applicant's manufacturing facility was inspected on January , 2008 and the facility was found to be in compliance with the Quality System Regulation (21 CFR 829).

XIII. APPROVAL SPECIFICATIONS

Directions for use: See attached labeling.

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

Postapproval Requirements and Restrictions: See approval order.

XIV. REFERENCES

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