SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Human Papillomavirus (HPV) DNA Detection Kit

Device Trade Name: BD Onclarity HPV Assay

Device Procode: MAQ

Applicant's Name and Address:

Becton Dickinson and Company
7 Loveton Circle
Sparks, MD 21152

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P160037/S017

Date of FDA Notice of Approval: May 14, 2024

The original PMA P160037 was approved on Feb. 12, 2018. A PMA supplement P160037/S008 was approved on Feb. 9, 2023. Based on the two submissions, the BD Onclarity HPV Assay is indicated for:

The BD Onclarity HPV Assay is a qualitative in vitro test for the detection of Human Papillomavirus in clinician-collected cervical specimens using an endocervical brush/spatula combination or broom and placed in a BD SurePath vial or placed in ThinPrep Pap Test PreservCyt Solution. The test utilizes amplification of target DNA by the Polymerase Chain Reaction (PCR) and nucleic acid hybridization for the detection of 14 high-risk (HR) HPV types in a single analysis. The test specifically identifies types 16, 18, 31, 45, 51, and 52 while reporting the other HR HPV types in groups (33/58, 35/39/68, and 56/59/66). The BD Onclarity HPV Assay is indicated for use for routine cervical cancer screening as per professional medical guidelines, including triage of ASC-US cytology, co-testing (or adjunctive screen) with cytology, and HPV primary screening of women to assess the risk for cervical precancer and cancer. Patients should be followed-up in accordance with professional medical guidelines, results from prior screening, medical history, and other risk factors.

The SSED to support the original PMA is available on the CDRH website and is incorporated by reference here.
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P160037

The approval order statement for P160037/S008 is available on the CDRH website and is incorporated by reference here.
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P160037S008

The current supplement was submitted to expand the indication for the BD Onclarity HPV Assay to include self-collected vaginal swab specimen in healthcare settings.

II. INDICATIONS FOR USE

The BD Onclarity HPV Assay is a qualitative in vitro test for the detection of high-risk (HR) Human Papillomavirus. The test utilizes amplification of target DNA by the Polymerase Chain Reaction (PCR) and nucleic acid hybridization for the detection of 14 HR HPV types in a single analysis. The test specifically identifies types 16, 18, 31, 45, 51, and 52 while reporting the other HR HPV types in groups (33/58, 35/39/68, and 56/59/66) in the specimens listed below.

Clinician-collected cervical specimens should be obtained using an endocervical brush/spatula combination or broom and placed in a BD SurePath vial or placed in ThinPrep Pap Test PreservCyt Solution.

Self-collected vaginal specimens, obtained in a healthcare setting, can be tested as an alternative specimen type when cervical sampling is either contraindicated or cervical specimens otherwise cannot be obtained.

The BD Onclarity HPV Assay is indicated for use for routine cervical cancer screening as per professional medical guidelines, including triage of ASC-US cytology, co-testing (or adjunctive screen) with cytology, and HPV primary screening of individuals with a cervix to assess the risk for cervical precancer and cancer. Patients should be followed-up in accordance with professional medical guidelines, results from prior screening, medical history, and other risk factors.

III. CONTRAINDICATIONS

None

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the BD Onclarity HPV Assay labeling.

V. DEVICE DESCRIPTION

The BD Onclarity HPV Assay is based on two major processing steps: 1) automated specimen preparation to homogenize the matrix, lyse cells, and extract cellular DNA; and 2) PCR amplification of target DNA sequences using primers and fluorescently-labeled detector probes for both HPV and human beta globin. The human beta globin serves as an internal control of the entire test by concurrently assessing specimen processing, extraction,

and amplification. The BD Onclarity HPV Assay uses HPV target regions in E6/E7 oncogenes for primers and probes.

The BD Onclarity HPV Assay uses real-time PCR technology. The detection of the target DNA is accomplished using TaqMan DNA probes that include a fluorescent dye at the 5' end and a quenching molecule at the 3' end of the oligonucleotide. The BD Onclarity HPV Assay utilizes fifteen probes labeled with one of four fluorescent dyes. Each dye is paired with one of two Black Hole Quencher molecules (BHQ Dye). The BD Onclarity HPV Assay reagents are dried in three individual PCR tubes that are capable of detecting 14 high risk HPV genotypes and a specimen-derived internal control, the human beta globin gene. These genotypes are reported either individually (16, 18, 31, 45, 51, 52) or as a genotype group (33/58, 56/59/66, and 35/39/68). Each of the three PCR tubes contains specific oligonucleotide sets to detect HPV genotype DNA and an oligonucleotide set to detect a region of the human beta globin gene.

The PCR primer and probe sequences, reagent formulations, detection method, result analysis algorithms and result interpretation stay the same for clinician-collected cervical specimen and self-collected vaginal swab specimen. Self-collected vaginal specimens are collected in a healthcare setting. The collected dry vaginal swab is transported to testing laboratory where swab is added to the BD Onclarity HPV Self Collection Diluent Tube (containing 3.0 mL of BD Onclarity HPV Self Collection Diluent which has the same composition as diluent for cervical specimen). There is no further dilution process for self-collected vaginal swab specimen.

The automated specimen preparation for the BD Onclarity HPV Assay is completed by the BD COR PX Instrument or by the BD Pre-Warm Heater and the BD Viper LT System. Testing on the BD COR System allows for automated sample aliquoting from BD SurePath vials or PreservCyt Solution to sample diluent tubes. Cervical specimens collected in BD SurePath Collection Vials or PreservCyt Solution and vaginal specimens collected in BD Onclarity HPV Self Collection Diluent are extracted using BD FOX Extraction to release cellular DNA. The purified cellular DNA solution from each extracted specimen is transferred into PCR tubes containing reagents which are then sealed to prevent contamination. Fluorescent detection of amplification occurs in four separate optical channels on the BD Viper LT System and the BD COR System. The test results are automatically generated by software on both systems.

Interpretation of Results

Interpretation of test results for the BD Viper system

All calculations are performed automatically by the BD Viper LT software. The presence or absence of clinically relevant HPV DNA is determined by the PCR cycle (Ct) at which the signal crosses a pre-established threshold. The assay will extract, amplify and detect a fragment of the human beta globin gene as an internal control to assess specimen processing, extraction, amplification, and to indicate the presence of PCR inhibitors. If the HPV-specific signal is greater than a cycle threshold, the internal control is utilized by the algorithm in the interpretation of the result. If the HPV-specific signal is less than or equal to a cycle threshold, the internal control is ignored by the algorithm. Please refer to the BD Viper LT System User's Manual HPV Addendum for additional information on results reporting.

Interpretation of High Risk HPV Genotype HPV Test Results for the BD Onclarity HPV Assay

High Risk HPV Result	Interpretation	Result	Report
HR ⊕←	Positive for High Risk HPV types	HPV HR Positive	HPV DNA detected by PCR.
HR ⊖	Negative for High Risk HPV types	HPV HR Negative	HPV DNA not detected by PCR.
~~IC~~	HPV DNA, if present, is not detectable	Internal Control Failure	Internal Control Failure. Repeat test from appropriate BD Onclarity HPV diluent tube[a] or obtain another specimen for testing.
~~ET~~	HPV DNA, if present, is not detectable	Extraction Transfer Failure	Extraction Transfer Failure. Repeat test from appropriate BD Onclarity HPV diluent tube[a] or obtain another specimen for testing.
~~LL~~	HPV DNA, if present, is not detectable.	Liquid Level Failure	Liquid Level Failure. Repeat test from appropriate BD Onclarity HPV diluent tube[a] or obtain another specimen for testing.
→⊛	HPV DNA, if present, is not detectable.	Error	Error. Repeat test from appropriate BD Onclarity HPV diluent tube[a] or obtain another specimen for testing.

[a] BD Onclarity HPV SurePath Diluent Tubes are for use with BD SurePath specimens. BD Onclarity HPV LBC Diluent Tubes are for use with PreservCyt specimens. BD Onclarity HPV Self Collection Diluent Tubes are for use with self-collected vaginal specimens.

Interpretation of Specific HPV Genotype Test Results for the BD Onclarity HPV Assay

HPV Genotype Result	Interpretation	Result
16 ⊕←	Positive for HPV type 16	HPV type 16 Positive
16 ⊖	Negative for HPV type 16	HPV type 16 Negative
18 ⊕←	Positive for HPV type 18	HPV type 18 Positive
18 ⊖	Negative for HPV type 18	HPV type 18 Negative
45 ⊕←	Positive for HPV type 45	HPV type 45 Positive
45 ⊖	Negative for HPV type 45	HPV type 45 Negative
P1 ⊕←	Positive for HPV types 33 and/or 58	HPV type 33 and/or 58 Positive
P1 ⊖	Negative for HPV types 33 and/or 58	HPV type 33 and/or 58 Negative
31 ⊕←	Positive for HPV type 31	HPV type 31 Positive
31 ⊖	Negative for HPV type 31	HPV type 31 Negative
P2 ⊕←	Positive for HPV types 56, 59 and/or 66	HPV type 56, 59 and/or 66 Positive
P2 ⊖	Negative for HPV types 56, 59 and/or 66	HPV type 56, 59 and/or 66 Negative
51 ⊕←	Positive for HPV type 51	HPV type 51 Positive
51 ⊖	Negative for HPV type 51	HPV type 51 Negative
52 ⊕←	Positive for HPV type 52	HPV type 52 Positive
52 ⊖	Negative for HPV type 52	HPV type 52 Negative
P3 ⊕←	Positive for HPV types 35, 39 and/or 68	HPV type 35, 39 and/or 68 Positive
P3 ⊖	Negative for HPV types 35, 39 and/or 68	HPV type 35, 39 and/or 68 Negative
▮═	HPV genotype result is available for purchase	Genotype result is locked
- -	HPV genotype result is not available for purchase	HPV Negative result, Internal Control failure, Liquid Level failure or Extraction Transfer failure.

Interpretation of test results for BD COR

All calculations are performed automatically by the BD COR System software. The presence or absence of clinically relevant HPV DNA is determined by the PCR cycle (Ct) at which the signal crosses a pre-established threshold. The assay will extract, amplify and detect a fragment of the human beta globin gene as an internal control to assess specimen processing, extraction, amplification, and to indicate the presence of PCR inhibitors. If the HPV-specific signal is greater than a cycle threshold, the internal control is utilized by the algorithm in the interpretation of the result. If the HPV-specific signal is less than or equal to a cycle threshold, the internal control is ignored by the algorithm.

Interpretation of High Risk HPV Genotype Test Results for the BD Onclarity HPV Assay

High Risk HPV Result	Interpretation	Result	Report
POS	Positive for High Risk HPV types	HPV HR Positive	HPV DNA detected by PCR.
NEG	Negative for High Risk HPV types	HPV HR Negative	HPV DNA not detected by PCR.
ICF	HPV DNA, if present, is not detectable	Internal Control Failure	Internal Control Failure. Repeat test from appropriate BD Onclarity™ HPV diluent tube[a] or obtain another specimen for testing.
ETF	HPV DNA, if present, is not detectable	Extraction Transfer Failure	Extraction Transfer Failure. Repeat test from appropriate BD Onclarity™ HPV diluent tube[a] or obtain another specimen for testing.
LLF	HPV DNA, if present, is not detectable.	Liquid Level Failure	Liquid Level Failure. Repeat test from appropriate BD Onclarity™ HPV diluent tube[a] or obtain another specimen for testing.
INC	Aborted sample set or sample	Incomplete	Sample processing is incomplete. No results are available for controls or samples. Repeat test from appropriate BD Onclarity™ HPV diluent tube[a] or obtain another specimen for testing.
QCF	Positive or Negative Control Failure	Quality Control Failure	No results are available for samples. Repeat test from appropriate BD Onclarity™ HPV diluent tube[a] or obtain another specimen for testing.

[a] BD Onclarity HPV SurePath Diluent Tubes are for use with BD SurePath specimens. BD Onclarity HPV LBC Diluent Tubes are for use with PreservCyt specimens. BD Onclarity HPV Self Collection Diluent Tubes are for use with vaginal self-collection specimens.

Interpretation of Specific HPV Genotype Test Results for the BD Onclarity HPV Assay

HPV Genotype Result	Interpretation	Result
16 POS	Positive for HPV type 16	HPV type 16 Positive
16 NEG	Negative for HPV type 16	HPV type 16 Negative
18 POS	Positive for HPV type 18	HPV type 18 Positive
18 NEG	Negative for HPV type 18	HPV type 18 Negative
45 POS	Positive for HPV type 45	HPV type 45 Positive
45 NEG	Negative for HPV type 45	HPV type 45 Negative
P1 POS	Positive for HPV types 33 and/or 58	HPV types 33 and/or 58 Positive
P1 NEG	Negative for HPV types 33 and/or 58	HPV types 33 and/or 58 Negative
31 POS	Positive for HPV type 31	HPV type 31 Positive
31 NEG	Negative for HPV type 31	HPV type 31 Negative
P2 POS	Positive for HPV types 56, 59, and/or 66	HPV types 56, 59, and/or 66 Positive
P2 NEG	Negative for HPV types 56, 59, and/or 66	HPV types 56, 59, and/or 66 Negative
51 POS	Positive for HPV type 51	HPV type 51 Positive
51 NEG	Negative for HPV type 51	HPV type 51 Negative
52 POS	Positive for HPV type 52	HPV type 52 Positive
52 NEG	Negative for HPV type 52	HPV type 52 Negative
P3 POS	Positive for HPV types 35, 39, and/or 68	HPV types 35, 39, and/or 68 Positive

P3 NEG	Negative for HPV types 35, 39, and/or 68	HPV types 35, 39, and/or 68 Negative
ICF	HPV DNA, if present, is not detectable	Internal Control Failure
- -	No result reported	Liquid Level failure or Extraction Transfer failure

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several alternatives for the detection of cervical cancer precursors, including testing by cytology alone, co-testing with HPV alongside or as a follow-up to cytology, or HPV testing with clinician-collected cervical specimen as a first line screening test for cervical cancer. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with a physician to select the method that best meets expectations and lifestyle.

The patient's age, medical history and thorough physical examination will provide further information on the risk of cervical disease, as well as the need for referral to colposcopy. The BD Onclarity HPV Assay should only be used in conjunction with this clinical information in accordance with appropriate clinical patient management guidelines.

VII. MARKETING HISTORY

The BD Onclarity HPV Assay is marketed as an in vitro diagnostic assay in the following countries: Australia, Brazil, Canada, Chile, China, Colombia, Guatemala, India, Israel, Korea, Malaysia, Mexico, New Zealand, Peru, Saudia Arabia, South Africa, Taiwan, Turkey, United States, Ukraine, Vietnam, and countries within the European Union, including Austria, Belgium, Denmark, France, Germany, Italy, Ireland, Luxemburg, Netherlands, Norway, Poland, Romania, Spain. Switzerland and United Kingdom. It has not been withdrawn from these markets for any reason related to the device's safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The following section outlines the potential adverse effects (e.g., complications) associated with the use of the BD Onclarity HPV Assay. As with any in vitro diagnostic test, the potential adverse effects are associated with incorrect test results or result interpretations. Failure of this device to perform as expected or failure to correctly interpret results may lead to incorrect HPV test results and subsequently, improper patient management decisions in cervical cancer screening. False negative results may lead to delays in the timely diagnosis of cervical cancer, allowing an undetected condition to worsen and potentially increasing morbidity and mortality. False positive results could lead to unnecessarily more frequent screening and procedures such as colposcopy and biopsy.

IX. SUMMARY OF NON-CLINICAL STUDIES

A. Laboratory Studies

1. Limit of Detection at the Clinical Cutoff for Vaginal Swab Specimen

HPV positive samples were prepared by spiking HPV16+ (SiHa), HPV18+ (HeLa) and HPV45+ (MS751) cell lines in clinical vaginal matrix. Additionally, similar HPV positive samples were prepared in simulated HPV-negative C33A cell matrix. The assay analytical sensitivity was found to be equivalent between these two matrices. The LoD of the remaining 11 genotypes were determined with plasmids spiked in C33A cell matrix. Studies were performed on both BD Viper LT and BD COR systems and results are the same between the two systems. The LoD values are presented in the table below.

Target	LoD (cell/mL or cp/mL)	95% CI	
		Lower	Upper
SiHa (HPV16)	9.7	7.7	13.4
HeLa (HPV18)	51	46	56
MS751 (HPV45)	305	284	343
HPV31	692	650	817
HPV33	1,376	1272	1451
HPV35	1,552	1317	1780
HPV39	1,531	1419	1685
HPV51	1,229	1155	1353
HPV52	833	744	934
HPV56	836	737	911
HPV58	2,990	2656	7818
HPV59	772	722	899
HPV66	701	646	767
HPV68	2,079	1995	2125

2. Interfering Substances

HPV negative and HPV positive samples (co-spiked with HPV16, HPV18 and HPV45 positive cell lines at 3xC_{95}) were tested in the presence of one of the potentially interfering substances that may be present in vaginal specimens as listed in the table below. Each potentially interfering substance was added into the HPV negative and positive samples and tested with the BD Onclarity HPV Assay.

The results are presented in the table below. The concentrations of the potentially interfering substances represent the highest level of the substance that did not show any interference with the BD Onclarity HPV Assay.

BD Self Collection Diluent	
Potential Interfering Substance	Concentration Tested
KY Vaginal Lubricant [a]	8% (w/v)
VCF Vaginal Contraceptive Film	3% (w/v)
VCF Vaginal Contraceptive Foam	10% (w/v)
Nonoxynol-9 Contraceptive Gel, 4%	1% (w/v)
Monistat 3[a]	1.8% (w/v)
Clotrimazole 7	10% (w/v)
Tioconazole Ointment, 6.5%	1% (w/v)
Clindamycin Vaginal Cream	9% (w/v)
Summer's Eve Douche	10% (v/v)
Zovirax (Acyclovir) Cream [a]	10% (w/v)
Vandazole Gel (Metronidazole Vaginal Gel, 0.75%)	10% (w/v)

Summer's Eve Deodorant	1% (w/v)
Replens Moisturizer [a]	2.8% (w/v)
Bovine Mucin [a]	7.8% (w/v)
Progesterone	20 ng/mL
Estradiol	1.2 ng/mL
Whole Blood[a]	1% (v/v)
Leukocytes	1x10^6 cells/mL
Semen	10% (v/v)
Estrace [a], 0.01%	7% (w/v)
Crinone [a], 4%	2% (w/v)
Preparation H [a]	6% (w/v)

a. This sub-set of substances was tested on the BD COR System because they may most challenge the pipetting system, e.g., gels, salves and mucins. Those substances that are soluble were not included because the assay chemistry remains unchanged.

There were seven substances that yielded false negative results when tested at concentrations higher than described in the table above: Whole Blood, Preparation H, Summer's Eve Deodorant, KY Jelly Personal Lubricant, Bovine mucin, Replens and Nonoxynol-9 Contraceptive Gel, 4%.

3. Vaginal Specimen Stability

Specimen stability study results demonstrated that vaginal specimen can be stored as dry swab at 2-30 °C, 2-8 °C or -20 °C for 30 days from the date of collection to the date of transfer to the BD Onclarity HPV Self Collection Diluent tube. After transfer to a BD Onclarity HPV Self Collection Diluent tube, the diluted specimen can be stored at 2-30 °C, 2-8 °C or -20 °C for 15 days before pre-warm. Specimens may be stored at 2-30 °C, 2-8 °C or -20 °C for seven (7) days after pre-warm but before testing. Tested specimens with punctured caps can be stored at 2–30 °C or 2-8 °C for seven (7) days without re-capping prior to repeat testing.

B. Animal Studies
Not Applicable

C. Additional Studies
Not Applicable

X. SUMMARY OF PRIMARY CLINICAL STUDY(IES)

The establishment of a reasonable assurance of safety and effectiveness of BD Onclarity HPV Assay with self-collected vaginal specimen is based on a clinical study, the extended VALHUDES study, conducted outside the U.S. This study is published and can be accessed via the following link: Performance of BD Onclarity HPV assay on FLOQSwabs vaginal self-samples - PMC (nih.gov). Data from this clinical study along with benefit-risk assessment were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

A total of 300 women were enrolled in the study between March 2021 and July 2021 in two Italian Colposcopy Centers. All subjects were referred to colposcopy as per previous screening to detect cell abnormality.

Self-collected vaginal specimen and clinician-collected cervical specimen were collected from each subject. All enrolled subjects were informed by the colposcopy staff on the study procedures and informed consent was collected. Each enrolled subject was supplied with a FLOQSwab and self-collection instruction. For each subject, self-collected vaginal specimen was collected first. The collected swab was immediately placed back into the provided plastic sheath and handed over to the healthcare provider. A cervical brush specimen using a Cervex-Brush (Rovers Medical Devices, The Netherlands) was collected by a gynecologist prior to undergoing colposcopy and the specimen was transferred into 20 ml of PreservCyt LBC medium (Hologic Inc., Bedford, MA, USA). As colposcopy was performed, a colposcopy-targeted biopsy was collected as per routine management of women with cervical lesions.

Cervical specimens and self-collected dry vaginal swabs were shipped to a testing laboratory. Upon arrival at the laboratory, each vaginal swab was broken into a BD Onclarity HPV Self Collection Diluent Tube containing 3.0 mL of BD Onclarity HPV Self Collection Diluent (BD Diagnostics, Sparks, MD, USA). For cervical specimen, 0.5 mL of LBC specimen in PreservCyt vial was transferred to the BD HPV LBC Diluent Tube containing 1.7 mL of medium (this medium is with the same composition as the BD Onclarity HPV Self Collection Diluent) as instructed in labeling. Both cervical and self-collected vaginal specimens were tested with BD Onclarity HPV assay on BD Viper LT.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the extended VALHUDES study was limited to patients who were referred for colposcopy based on previous abnormal cytology results.

   Patients were not permitted to enroll in the extended VALHUDES study if they met any of the following exclusion criteria:

   1) women younger than 25 years

   2) women older than 64 years

   3) hysterectomized women

   4) women with known pregnancy

2. Follow-up Schedule

No follow-up was scheduled pertaining to the establishment of performance of the assay on self-collected vaginal specimen. The study protocol did not include any follow-up

observations of enrolled subjects.

3. Clinical Endpoints

With regards to safety, as an in vitro diagnostic test, the BD Onclarity HPV Assay involves sampling cells from the vagina using a swab. The test, therefore, presents no more safety hazard to an individual being tested than other tests where vaginal samples are collected in this manner (e.g., STI devices). Safety issues regarding false positive and negative test results are discussed in section XIV part B and C.

With regards to effectiveness, the concordance between Clinician-collected Cervical (CC) specimen and Self-collected Vaginal (SV) specimen was evaluated. Further, the clinical sensitivity in detecting ≥CIN2 and ≥CIN3, clinical specificity and false positive rate in detecting ≤CIN1, for both self-collected vaginal specimen and cervical specimen were calculated. Additionally, ratio of sensitivity (SV:CC), ratio of specificity (SV:CC) and ratio of false positive rate (SV:CC) were calculated.

B. Accountability of PMA Cohort

Of 300 patients enrolled in the study, 10 subjects (3.3%) were excluded from the study due to unsatisfactory biopsy result. Out of the remaining 290 subjects, 181 subjects had biopsy collected and had histology result. One (1) cervical specimen and three (3) self-collected vaginal specimens have invalid HPV test results. Therefore, the concordance calculation was based on results from 286 subjects. The clinical sensitivity, specificity and false positive rate calculations were based on results from 289 valid subject results for cervical specimen and 287 valid subject results for self-collected vaginal specimen.

C. Study Population Demographics and Baseline Parameters

Characteristics of the study population are present in the table below. Sixty-two percent of women underwent biopsy or endocervical curettage (181/290) and had subsequent histology evaluation. A total of 207 (207/290, 71.4%) women had ≤CIN1 or a colposcopy without a histological outcome. Resulting histology indicated 83 women with ≥CIN2 (83/290; 28.6%) including 48 women with ≥CIN3 (48/290; 16.6%). The HR HPV positivity rates on different age groups are similar when comparing self-collected vaginal specimen to cervical specimen.

		Cervical HR HPV	Vaginal HR HPV	Disease outcome		
Age category (years)	**Participants N (%)**	**Positive N (%)**	**Positive N (%)**	**≤CIN1 N (%)**	**≥CIN2 N (%)**	**≥CIN3 N (%)**
<30	46 (15.9)	38 (19.9)	39 (19.0)	27 (13.0)	19 (22.9)	12 (25.0)
30–39	96 (33.1)	64 (33.5)	73 (35.6)	66 (31.9)	30 (36.1)	19 (39.6)
40–49	81 (27.9)	52 (27.2)	51 (24.9)	58 (28.0)	23 (27.7)	14 (29.2)
50–59	57 (19.7)	31 (16.2)	35 (17.1)	48 (23.2)	9 (10.8)	1 (2.1)
60+	10 (3.5)	6 (3.1)	7 (3.4)	8 (3.9)	2 (2.4)	2 (4.2)

Total	290 (100.0)	191 (100.0)	205 (100.0)	207 (100.0)	83 (100.0)	48 (100.0)
		Cervical HR HPV	**Vaginal HR HPV**	**Disease outcome**		
Colposcopy center	**Participants N (%)**	**Positive N (%)**	**Positive N (%)**	**≤CIN1 N (%)**	**≥CIN2 N (%)**	**≥CIN3 N (%)**
Milan	149 (51.4)	110 (57.6)	118 (57.6)	79 (38.2)	70 (84.3)	44 (91.7)
Sassari	141 (48.6)	81 (42.4)	87 (42.4)	128 (61.8)	13 (15.7)	4 (8.3)

D. Safety and Effectiveness Results

1. Safety Results

   With regards to safety, as an in vitro diagnostic test, the BD Onclarity HPV Assay involves sampling cells from the vagina using a swab. The test, therefore, presents no more safety hazard to an individual being tested than other tests where vaginal samples are collected in this manner.

   Safety issues regarding false positive and negative test results are discussed in section XIV part B and C.

   Adverse effects that occurred in the PMA clinical study:

   The only intervention requested as part of the study was the collection of minimally invasive self-collected vaginal specimen and no adverse effect regarding self vaginal collection was observed during the study. Treatment of cervical precancer and potential adverse events related to colposcopy (potentially resulting from local clinical practice protocols) were managed by the clinician offering the treatment and were not evaluated within the study as dictated by the study scope.

2. Effectiveness Results

   In the study, there were 286 patients with valid CC and valid SV results. Data are presented in the table below and Positive Percent Agreement (PPA) and Negative Percent Agreement (NPA) were calculated along with two-sided 95% confidence intervals (95% CI).

   In addition, sensitivity, specificity as well as false positive rate of BD Onclarity HPV Assay in detecting cervical precancer (no >CIN3 was observed in this study) on SV specimen and the CC specimen, as well as ratio of sensitivity (SV:CC), ratio of specificity (SV:CC) and ratio of false positive rate (SV:CC) along with two-sided 95% CI are presented in the following tables.

   For detection of HR HPV, the PPA and NPA of SV specimen as compared to CC specimen are 96.3% and 76.5%, respectively.

   The sensitivities of the assay for detecting ≥CIN2 with SV and CC are 90.4% and 89.2%, respectively, with a ratio of sensitivity (SV:CC) of 1.01. The sensitivities

of the assay for detecting ≥CIN3 with both SV and CC are 91.7%, with a ratio of sensitivity (SV:CC) of 1.00.

The false positive rate of the assay with SV and CC are 63.7% and 56.8%, respectively, with a ratio of false positive rate (SV:CC) of 1.12. Out of the 21 subjects tested HR HPV positive by SV but negative by CC among ≤CIN1 individuals, 19 were "12 Other HR HPV" positive. Based on the clinical management guidelines, "12 Other HR HPV" positive subjects will be referred to a follow-up cytology test.

Total		**CC**			
		HPV16 or 18	12 Other HR HPV	HR HPV Negative	Total
SV	HPV16 or 18	76	12	3	91
	12 Other HR HPV	0	93	20	113
	HR HPV Negative	2	5	75	82
	Total	78	110	98	286
PPA (HR HPV)=96.3% (181/188); 95% CI: (92.5%; 98.2%) PPA (HPV 16 or 18)=97.4% (76/78); 95% CI: (91.1%; 99.3%) PPA (12 Other HR HPV)=84.5% (93/110); 95% CI: (76.6%; 90.1%) NPA (HR HPV)=76.5% (75/98); 95% CI: (67.2%; 83.8%)					

≥ CIN2		**CC**				
		HPV16 or 18	12 Other HR HPV	HR HPV Negative	Invalid	Total
SV	HPV16 or 18	46	3	1	0	50
	12 Other HR HPV	0	24	1	0	25
	HR HPV Negative	1	0	7	0	8
	Invalid	0	0	0	0	0
	Total	47	27	9	0	83
Sensitivity (SV)= 90.4% (75/83); 95% CI: (82.1%; 95.0%) Sensitivity (CC)=89.2% (74/83); 95% CI: (80.7%; 94.2%) Ratio of sensitivity (SV:CC)=1.01 (90.4%/89.2%); 95% CI: (0.97; 1.06)						

≥CIN3*		CC				
		HPV16 or 18	12 Other HR HPV	HR HPV Negative	Invalid	Total
SV	HPV16 or 18	33	2	1	0	36
	12 Other HR HPV	0	8	0	0	8
	HR HPV Negative	1	0	3	0	4
	Invalid	0	0	0	0	0
	Total	34	10	4	0	48

Sensitivity (SV)=91.7% (44/48); 95% CI: (80.4%; 96.7%)
Sensitivity (CC)= 91.7% (44/48); 95% CI: (80.4%; 96.7%)
Ratio of sensitivity (SV: CC)=1.00 (91.7%/91.7%); 95%CI: (0.94; 1.06)
* no >CIN3 case was observed in the study.

≤CIN1		CC				
		HPV16 or 18	12 Other HR HPV	HR HPV Negative	Invalid	Total
SV	HPV16 or 18	30	9	2	0	41
	12 Other HR HPV	0	69	19	1	89
	HR HPV Negative	1	5	68	0	74
	Invalid	1	2	0	0	3
	Total	32	85	89	1	207

Specificity (SV)=36.3% (74/204); 95% CI: (30.0%; 43.1%)
Specificity (CC)=43.2% (89/206); 95% CI: (36.6%; 50.0%)
Ratio of specificity (SV:CC)=0.84 (36.3%/43.2%); 95% CI: (0.73; 0.94)

False positive rate (SV)=63.7% (130/204); 95% CI: (56.9%; 70.0%)
False positive rate (CC)=56.8% (117/206); 95% CI: (50.0%; 63.4%)
Ratio of false positive rate (SV:CC)=1.12 (63.7%/56.8%); 95% CI: (1.02; 1.22)

XI. FINANCIAL DISCLOSURE

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included five investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XII. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

None

XIII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

Device did not go to Panel. This PMA was not referred to the Microbiology Panel, an FDA advisory committee, for review and recommendation because this is the same assay using similar technology that has been reviewed by this panel.

XIV. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The sensitivity of the BD Onclarity HPV Assay with self-collected vaginal specimen placed in BD Onclarity HPV Self Collection Diluent has been demonstrated in the studied population (women referred to colposcopy).

B. Safety Conclusions

The risks of the device are based on the clinical data to support PMA approval as described above. The ratio of false positive rate (SV:CC) is 1.12, suggesting that the false positive rate of the assay based on self-collected vaginal specimen is higher than the false positive rate based on clinician-collected cervical specimen for the studied population (women referred to colposcopy). The main risk associated with false positive HR HPV results based on self-collected vaginal specimen is unnecessary colposcopy procedures. This risk is considered mostly mitigated due to the following.

Although colposcopies are invasive procedures that can be associated with patient inconvenience. It is anticipated that some of the risks associated with colposcopy (in particular the pain, discomfort and bleeding or more rarely infection associated with cervical biopsies) may be mitigated by the fact that biopsies would not be performed unless abnormal lesions are observed on examination, in which case the colposcopy may have been warranted. Overall, colposcopy is a generally safe and well-tolerated procedure with rare complications (i.e., infection, bleeding).

Additionally, certain endogenous and exogenous substances may interfere with the performance of the assay in self-collected vaginal specimens when present at concentrations greater than those specified in the result table presented for the Interfering Substances study above. These potential interfering substances include whole blood, Preparation H, Summer's Eve Deodorant, KY Jelly Personal Lubricant, Bovine mucin, Replens and Nonoxynol-9 Contraceptive Gel, 4%. Limitations regarding the potential risk of false negative results are included in the device labeling as a mitigation.

C. Benefit-Risk Determination

The utilization of self-collected vaginal specimen with the BD Onclarity HPV Assay will allow patients to self-collect vaginal specimen in a healthcare setting under the oversight of trained healthcare personnel, which may help improve cervical cancer screening coverage for the unscreened/underscreened women in the United States. This new specimen type may make it more feasible for individuals to collect specimens who

previously, due to patient convenience, medical comorbidities, or other factors, had not participated in cervical cancer screening with clinician-collected cervical specimens.

The risk associated with self-collected vaginal specimen based on the studied population may be the higher false positive rate in detecting cervical disease. In addition to what is described above, the implementation of the following strategies will help mitigate the potential risks. These include: 1) The self-collected vaginal specimen may be considered as an alternative specimen type when clinician-collected cervical specimen cannot be obtained; 2) Post-approval studies to validate the performance of self-collected vaginal swab specimen. Additionally, professional guideline recommendations may further mitigate the risk(s) for currently screened women by helping clinicians appropriately counsel patients on the benefits/risks of vaginal versus cervical screening approaches.

1. Patient Perspective
This submission did not include specific information on patient perspectives for this device.

In conclusion, given the available information above, the data support that the self-collected vaginal specimen can be used as an alternative specimen type for the BD Onclarity HPV Assay when clinician-collected cervical specimen cannot be obtained, and the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of the BD Onclarity HPV Assay when used in accordance with the indications for use.

The data in this application support the reasonable assurance of safety and effectiveness of the BD Onclarity HPV Assay with self-collected vaginal specimen when used in accordance with the indications for use. The data from the nonclinical studies demonstrated acceptable analytical sensitivity of the BD Onclarity HPV Assay with self-collected vaginal specimen when used according to instructions for use, warnings and precautions, and limitations sections of the labeling. The clinical studies and performance analysis of the clinical data in this application have shown that the assay is safe and effective for use with self-collected vaginal specimen according to the indications for use and directions for use in the labeling.

XV. CDRH DECISION

CDRH issued an approval order on May 14, 2024. The final clinical conditions of approval cited in the approval order are described below.

The post-approval study, identified as "SHIP Sub-Protocol LMI-001-A-S01" will be coordinated by NCI Cervical Center as part of the NCI Cervical Cancer ‘Last Mile’ Initiative: Self-collection for HPV testing to Improve Cervical Cancer Prevention (SHIP) Trial. The study will include 500 or more individuals with a cervix, 25 years or older,

with referrals to colposcopy based on previous positive HPV test or abnormal cytology results. The study will provide additional data regarding clinical performance of the BD Onclarity HPV Assay with vaginal specimens in a U.S. population. The clinical sensitivity, clinical specificity and false positive rate in detecting precancer/cancer as well as the corresponding ratio between vaginal and cervical specimens will be evaluated. Additionally, the concordance of the BD Onclarity HPV Assay results between the two specimen types will be evaluated.

From the date of study protocol approval, you must meet the following timelines for study subject enrollment:

- First subject enrolled within 4 months
- 20% of subjects enrolled within 5 months
- 50% of subjects enrolled within 6 months
- 100% of subjects enrolled within 7 months

In addition, you must submit separate periodic reports on the progress of SHIP Sub-Protocol LMI-001-A-S01 as follows:

- PAS Progress Reports every six (6) months until subject enrollment has been completed.
- If any enrollment milestones are not met, you must begin submitting quarterly enrollment status reports every 3 months in addition to your periodic (6-month) PAS Progress Reports, until FDA notifies you otherwise.
- Submit the Final PAS Report three (3) months from study completion (i.e., last subject's study visit date).

XVI. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.