SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

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

Device Trade Name: cobas HPV

Device Procode: MAQ

Applicant's Name and Address:

Roche Molecular Systems, Inc.
4300 Hacienda Drive
Pleasanton, CA 94588-2722 USA

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P190028/S009

Date of FDA Notice of Approval: May 14, 2024

The original PMA P190028 was approved on April 3, 2020. A PMA supplement, P190028/S007 were approved on October 4, 2023. Based on the two submissions, the cobas HPV is indicated for:

cobas HPV for use on the cobas 5800/6800/8800 Systems (cobas HPV) is a qualitative *in vitro* test for the detection of Human Papillomavirus in clinician-collected cervical specimens using an endocervical brush/spatula or broom and placed in the ThinPrep Pap Test PreservCyt Solution. This test detects the high-risk HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68.

cobas HPV 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=P190028

The approval order statement for P100020/S007 is available on the CDRH website and is incorporated by reference here.

https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P190028S007

The current supplement was submitted to expand the indication for the cobas HPV test to include self-collected vaginal swab specimen in healthcare setting.

II. INDICATIONS FOR USE

cobas HPV for use on the cobas 5800/6800/8800 Systems (cobas HPV) is a qualitative *in vitro* test for the detection of high-risk Human Papillomavirus. This test detects the high-risk HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68 in the specimens listed below.

Clinician-collected cervical specimens should be obtained using an endocervical brush/spatula or broom and placed in the 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 samples otherwise cannot be obtained.

cobas HPV 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 cobas HPV labeling.

V. DEVICE DESCRIPTION

cobas HPV is a qualitative real-time PCR test that detects 14 high-risk HPV genotypes. Of 14 HPV genotypes, 13 HPV genotypes are classified as carcinogenic or high-risk (HR): 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, and an additional genotype, 66, that is classified as "possibly carcinogenic" based on its relatively low prevalence in invasive cervical carcinoma. cobas HPV uses primers to define a sequence of approximately 200 nucleotides within the polymorphic L1 region of the HPV genome. A pool of HPV primers present in the Master Mix is designed to amplify HPV DNA from 14 high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68). The test includes a primer pair that amplifies the human β-globin gene as an internal control to monitor the entire sample preparation and PCR amplification process (330

base pair amplicon). Fluorescent oligonucleotide probes bind to polymorphic regions within the sequence defined by these primers. In addition, the test utilizes a low titer positive and a negative control.

cobas HPV consists of:

- cobas 5800/6800/8800 Systems
- cobas HPV assay specific analysis package (ASAP) software
- cobas HPV reagents in cassettes
- cobas HPV Positive Control Kit
- cobas Buffer Negative Control Kit
- Specimen preparation reagents (cobas omni Reagents)

cobas HPV is based on fully automated sample preparation (nucleic acid extraction and purification) followed by PCR amplification and detection. The cobas 5800/6800/8800 Systems consist of the sample supply module, the transfer module, the processing module, and the analytic module. Automated data management is performed by the cobas 5800/6800/8800 software, which assigns test results for all tests as positive, negative or invalid. Results can be reviewed directly on the system screen, exported, or printed as a report.

Principle of Procedure

1. Sample Preparation (Nucleic Acid Extraction and Purification)
   Nucleic acid from a patient sample is released upon addition of proteinase and lysis reagent to the sample. The released nucleic acid binds to the silica surface of the added magnetic glass particles. Unbound substances and impurities, such as denatured protein, cellular debris, and potential PCR inhibitors are removed with subsequent wash steps, and purified nucleic acid is eluted from the magnetic glass particles with elution buffer at elevated temperature. External controls (positive and negative) are processed in the same way with each cobas HPV run.

2. Nucleic Acid Amplification
   A thermostable DNA polymerase enzyme is used for PCR amplification. The HPV and β-globin sequences are amplified simultaneously utilizing a universal PCR amplification profile with predefined temperature steps and number of cycles. The master mix includes deoxyuridine triphosphate (dUTP), instead of deoxythimidine triphosphate (dTTP), which is incorporated into the newly synthesized DNA (amplicon). Any contaminating amplicon from previous PCR runs are eliminated by the AmpErase enzyme, which is included in the PCR master mix, during the first thermal cycling step. However, newly formed amplicons are not eliminated since the AmpErase enzyme is inactivated once exposed to temperatures above 55°C.

3. Nucleic Acid Detection
   The cobas HPV master mix contains detection probes specific for twelve High Risk HPV target sequences, one detection probe specific for the HPV16 target sequence, one detection probe specific for the HPV18 target sequence and one for β-globin. The amplified signal from twelve high-risk HPV types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) is detected using the same fluorescent dye while HPV16, HPV18, and β-

globin signals are each detected with their own dedicated fluorescent dye. When not bound to the target sequence, the fluorescent signal of the intact probes is suppressed by a quencher dye. During the PCR amplification step, hybridization of the probes to the specific single-stranded DNA template results in cleavage of the probe by the 5' to 3' exonuclease activity of the DNA polymerase resulting in separation of the reporter and quencher dyes and the generation of a fluorescent signal. With each PCR cycle, increasing amounts of cleaved probes are generated and the cumulative signal of the reporter dye increases concomitantly. Real-time detection and discrimination of PCR products is accomplished by measuring the fluorescence of the released reporter dyes for the HPV targets and β-globin, respectively.

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 when a cervical specimen cannot be obtained. The self-collected vaginal specimen is suspended in PerservCyt fluid by a trained professional and transported to testing laboratory.

Interpretation of Test Results

Results and their corresponding interpretation for detecting overall HR HPV and HPV-Genotyping are shown in the tables below:

Target 1	Target 2	Target 3	Interpretation
HR HPV Positive			Specimen is positive for the DNA of any one of, or combination of, the following high risk HPV types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68.
HR HPV Negative			HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 DNA were undetectable or below the pre-set threshold.
Invalid	<Blank>	<Blank>	The result for HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68 is invalid.

Target 1	Target 2	Target 3	Interpretation
Other HR HPV Positive			Specimen is positive for the DNA of any one of, or combination of the following high risk HPV types: 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68.
Other HR HPV Negative			HPV types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68 were undetectable or below the pre-set threshold.
Invalid			The result for HPV types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 is invalid.
	HPV 16 Positive		Specimen is positive for HPV type 16 DNA.

	HPV 16 Negative		HPV type 16 DNA was undetectable or below the pre-set threshold.
	Invalid		The result for HPV type 16 is invalid.
		HPV 18 Positive	Specimen is positive for HPV type 18 DNA.
		HPV 18 Negative	HPV type 18 DNA was undetectable or below the pre-set threshold.
		Invalid	The result for HPV type 18 is invalid.

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 cobas HPV should only be used in conjunction with this clinical information in accordance with appropriate clinical patient management guidelines.

VII. MARKETING HISTORY

The product is currently distributed/marketed in forty-one countries. The product has been available in the U.S. since 2020. The product has not been withdrawn to date from the market in any country for reasons related to the safety or effectiveness of the device.

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 cobas HPV. 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 many patients to unnecessarily undergo more frequent screening and potentially invasive 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 Specimens

The LoD at the clinical cutoff of high risk HPV genotypes HPV16 and HPV18 in vaginal matrix was determined for the cobas HPV. The LoDs were assessed using HPV positive cell lines SiHa (HPV16) and HeLa (HPV18) in the background of pooled HPV negative self-collected vaginal specimens collected in PreservCyt Solution. Cell lines were diluted to concentrations targeting above, below, and at the expected LoD levels. A minimum of 27 replicates was tested for each cell line level for each of 2 reagent lots. A total of six independent dilutions was prepared over a period of three days and tested using one 5800, one 6800, and one 8800 system. The LoD at the clinical cutoff is the level of HPV DNA in the sample that has positive test results (above the clinical cutoff) at least 95% of the time. The table below contains results from the reagent lot producing the most conservative (highest) LoD in the analysis.

HPV Type	Concentration (cells/ml)	Number of Positive/tested	Mean Ct	% Positives
SiHa (HPV16)	32	27/27	34.0	100%
	16	27/27	34.8	100%
	8	22/27	35.4	81.5%
HeLa (HPV18)	32	27/27	32.9	100%
	16	25/27	33.6	92.6%
	8	27/27	34.3	100%

2. Interfering Substances

HPV16/HPV18 positive and HPV16/HPV18 negative sample pools of self-collected vaginal specimens were used to assess the effects of endogenous and exogenous interfering substances that could potentially be present in vaginal specimens. The concentrations of endogenous and exogenous substances tested represent conditions that could occur during specimen collection and are listed in the table below. Interference was not seen for substances tested with the exception of RepHresh Odor Eliminating pH Balancing Gel at 1.25% (w/v) and Dove Advanced Care Clear Finish Antiperspirant Dry Spray at 0.2% and 0.02% (w/v).

Potential Interfering Substance	Concentration Tested	Interference Observed
Beta Estradiol	0.07 mg/mL	None
Biotin	3.87 µg/mL	None
Mucin	0.8% (w/v)	None
PBMC	10^6 cells/mL	None
Progesterone	0.07 mg/mL	None
Seminal fluid	5% (v/v)	None
Whole Blood	1.5%, 10% (v/v)	None
Abreva Cold Sore Cream	0.25% (w/v)	None
Preparation H Hemorrhoidal Ointment	0.25% (w/v)	None
RepHresh Odor Eliminating pH Balancing Gel	1.25% (w/v)	Yes
Summer's Eve Povidone-Iodine Medicated Douche	0.25% (w/v)	None
Summer's Eve Cleansing Wash	0.40% (w/v)	None
Dove Advanced Care Clear Finish Antiperspirant Dry Spray (0% alcohol)	0.20%, 0.02% (w/v)	Yes

3. Specimen Stability

Specimen stability study results demonstrated that vaginal specimens, collected in PreservCyt, can be stored at 2 – 30˚C for 30 days from the date of collection.

B. <u>Animal Studies</u>
Not Applicable

C. <u>Additional Studies</u>
Not Applicable

X. SUMMARY OF PRIMARY CLINICAL STUDY(IES)

To establish a reasonable assurance of safety and effectiveness for the cobas HPV with the self-collected vaginal specimen, the applicant performed a clinical study to determine the agreements between self-collected vaginal specimens and clinician-collected cervical specimens in detecting high-risk HPV nucleic acid during routine cervical cancer screening in the US. The clinical study evaluated self-collection using the FLOQswab #552C.RM (manufactured by Copan in Italy) or the Evalyn Brush (manufactured by Rovers in Netherlands). Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

1,528 participants were enrolled between June 2021 and December 2021 at eight Planned Parenthood Gulf Coast, Inc. health centers locations (two in Louisiana and four in Texas). Women who were attending a Planned Parenthood Gulf Coast, Inc. health center were invited to participate in the clinical study, if they did not meet the exclusion criteria.

First, each participant self-collected a vaginal sample using either the Evalyn Brush (cohort 1) or the FLOQswab #552C.RM (cohort 2). Self-collected samples were then placed in 20 mL of methanol-based medium by a health care provider. Next, a clinician collected a cervical sample using the broom-like collection device, as per the approved instructions, and placed it in the same medium type used to dilute the self-collected samples. Samples were shipped to RMS Pleasanton for testing. Each paired sample was tested using the cobas HPV.

1. Clinical Exclusion Criteria
   Patients were not permitted to enroll if they met any of the following exclusion criteria:
   - Women less than 18 years old
   - Pregnant women
   - Women who were menstruating on the day of the visit
   - Women with hysterectomies
   - Individuals unable to provide written consent
   - Individuals who have used creams/ointments that contain carbomer(s) for example: Metronidazole Vaginal Gel, Replens, RepHresh Odor Eliminating Vaginal Gel and RepHresh Clean Balance Feminine Freshness Kit
   - Individuals who had an exam where a lubricant containing carbomer has been used on the speculum

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 participants.

3. Clinical Endpoints

With regards to safety, as an *in vitro* diagnostic test, the cobas HPV test 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 Positive Percent Agreements (PPA) for HR HPV, HPV16 and HPV18 combined (HPV16/18), and 12 other HR HPV, and Negative Percent Agreement (NPA), along with two-sided 95% confidence intervals (95% CI), were calculated for the self-collected vaginal samples against the paired clinician-collected cervical samples.

B. Accountability of PMA Cohort

1,528 participants were enrolled in the study. Current guidelines recommend primary HPV screening for individuals 25 years and older, therefore 461 participants were excluded due to being under the age of 25. The accountability of the remaining 1,067 participants is presented in the table below.

Collection Device Cohort	Total enrolled	Excluded due to invalid cervical result	Excluded due to invalid vaginal result	Total valid paired results
1	556	0	24	532
2	511	2	22	487

C. Study Population Demographics and Baseline Parameters

Characteristics of the evaluable study population are present in the tables below.

Evalyn Brush

Age Category	Participants	Cervical HR HPV	Vaginal HR HPV
		Pos N (%)	Pos N (%)
25 - 29	199 (37.4%)	65 (32.7%)	71 (35.7%)
30 – 39	236 (44.4%)	65 (27.5%)	64 (27.1%)
40 – 49	88 (16.5%)	13 (14.8%)	22 (25.0%)
50+	9 (1.7%)	2 (22.2%)	2 (22.2%)
Total	532 (100%)	145 (27.3%)	159 (29.9%)

FLOQSwab

Age Category	Participants	Cervical HR HPV Pos N (%)	Vaginal HR HPV Pos N (%)
25 - 29	191 (39.2%)	51 (26.7%)	56 (29.3%)
30 – 39	215 (44.1%)	55 (25.6%)	54 (25.1%)
40 – 49	63 (12.9%)	9 (14.3%)	14 (22.2%)
50+	18 (3.7%)	0 (0.0%)	1 (5.6%)
Total	487 (100%)	115 (23.6%)	125 (25.7%)

D. Safety and Effectiveness Results

1. Safety Results

With regards to safety, as an *in vitro* diagnostic test, the cobas HPV involves sampling cells from the vagina using a swab or brush. 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.B-C.

Adverse effects that occurred in the PMA clinical study:

The only additional intervention requested as part of the study was the collection of minimally invasive self-collected vaginal specimen. 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 532 participants in cohort 1 with valid paired results and 487 participants in cohort 2 with valid paired results. PPAs and NPAs, along with 95% CIs, are calculated in the tables below.

For cohort 1, the rate of invalid results for the self-collected and clinician-collected specimens were 4.3% and 0.0%, respectively. For cohort 2, the rate of invalid results for the self-collected and clinician-collected specimens were 4.3% and 0.4%, respectively.

Evalyn Brush		Clinician-Collected Cervical Specimen			
		HPV16 or 18	HR HPV "12 Other"	HR HPV Negative	Total
Self-Collected Vaginal Specimen	HPV16 or 18	26	1	8	35
	HR HPV "12 Other"	0	97	27	124
	HR HPV Negative	0	21	352	373
	Total	26	119	387	532
14 HR HPV PPA = 85.5% (124/145) (95% CI: 78.9% - 90.3%) HPV 16/18 PPA = 100% (26/26) (95% CI: 87.1% - 100%) 12 other HR HPV PPA = 81.5% (97/119) (95% CI: 73.6% - 87.5%) NPA = 91.0% (352/387) (95% CI: 87.7% - 93.4%)					

FLOQSwab #552C.RM		Clinician-Collected Cervical Specimen			
		HPV16 or 18	HR HPV "12 Other"	HR HPV Negative	Total
Self-Collected Vaginal Specimen	HPV16 or 18	14	0	3	17
	HR HPV "12 Other"	0	78	30	108
	HR HPV Negative	1	22	339	362
	Total	15	100	372	487
14 HR HPV PPA = 80.0% (92/115) (95% CI: 71.8% - 86.3%) HPV 16/18 PPA = 93.3% (14/15) (95% CI: 70.2% - 98.8%) 12 other HR HPV PPA = 78.0% (78/100) (95% CI: 68.9% - 85.0%) NPA = 91.1% (339/372) (95% CI: 87.8% - 93.6%)					

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 one investigator. 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

The applicant provided a summary of peer-reviewed research articles that each evaluated the cobas HPV when testing self-collected vaginal samples. The literature review is supportive of a favorable benefit-risk profile for self-collected vaginal specimens, used as an alternative specimen type for the cobas HPV, when clinician-collected cervical specimen cannot be obtained.

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 agreements for self-collected vaginal specimens compared with paired clinician-collected cervical specimens has been established using the cobas HPV test in the studied population. Based on the agreements obtained from the study described above, self-collected vaginal specimens appear less sensitive and specific in comparison to clinician-collected cervical specimens. However, in the study, the PPA between self-collected vaginal specimens and clinician-collected cervical specimens was higher for the detection of HPV 16/18 infections than for the detection of 12 Other HR HPV. Given that HPV 16/18 infections carry the greatest likelihood for development of cervical disease, false negative 12 Other HR HPV results are associated with a lower risk of missed cervical disease cases than false negative HPV 16/18 results.

B. Safety Conclusions

The risks of the device are based on the clinical data to support PMA approval as described above. Due to the lower PPA between self-collected vaginal specimens and clinician collected cervical specimens, the primary risk associated with self-collected vaginal specimens may arise if regularly-screened individuals electively switch from clinician-collected cervical specimens to self-collected vaginal specimens, which could result in potential missed cervical disease cases that could have otherwise been detected and prevented using the current standard of care (i.e., clinician-collected cervical specimens). This risk could be partially-mitigated by the observation in the clinical study that the lower PPA of self-collected vaginal specimens appears driven by more false negatives for 12 Other HR HPV than by the more clinically-significant HPV16 and HPV18. This risk is considered mostly mitigated due to the implementation strategies described in section XIV part C.

Another risk associated with the lower NPA between self-collected vaginal specimens and clinician collected cervical specimens is the potential for an individual to undergo unnecessary colposcopy procedures. This risk is also 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 RepHresh Odor Eliminating pH Balancing Gel and Dove Advanced Care Clear Finish Antiperspirant Dry Spray. 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 cobas HPV will allow patients to self-collect vaginal specimens in a healthcare setting under the oversight of trained healthcare personnel, which may help improve cervical cancer screening coverage particularly for unscreened/underscreened individuals 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 false results with self-collected vaginal specimens in comparison to clinician-collected cervical specimens. In addition to what is described above, the implementation of the following strategies will help mitigate the potential risks. These include: 1) Description in the Intended Use: 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 individuals 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 cobas HPV 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 cobas HPV when used in accordance with the indications for use.

The data in this application support the reasonable assurance of safety and effectiveness of the cobas HPV 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 cobas HPV 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 indication 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 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 contains two protocols, the "SHIP Sub-Protocol LMI-001-A-S02" and "SHIP Sub-Protocol LMI-001-A-S03", each designed to evaluate the performance of a specific self-collection device with the cobas HPV. Each protocol will enroll at least 500 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 cobas HPV 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 cobas HPV results between the two specimen types will be evaluated. The protocols were received by FDA via email dated May 5, 2024.

For each study protocol, from the date of the PMA approval letter, you must meet the following timelines for study subject enrollment:

- First subject enrolled within 4 months
- 20% of subjects enrolled within 6 months
- 50% of subjects enrolled within 8 months
- 100% of subjects enrolled within 12 months

In addition, for each study protocol, you must submit separate periodic reports on the progress of the study as follows:

- PAS Progress Reports every six (6) months until subject enrollment has been completed, and annually thereafter, from the date of the PMA approval letter, unless otherwise specified by FDA.
- 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 last follow-up 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.