SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

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

Device Trade Name: cobas HPV test

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: P100020/S055

Date of FDA Notice of Approval: May 14, 2024

The original PMA P100020 was approved on April 19, 2011. Four PMA supplements, P100020/S008, P100020/S017, P100020/S025, P100020/S049 were approved on April 24, 2014, July 7, 2016, July 2, 2018, and March 4, 2020 respectively. Based on the four submissions, the cobas HPV test is indicated for:

The cobas HPV Test for use on the cobas 4800 System (cobas HPV Test) 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 or using a cervical broom and placed in SurePath Preservative Fluid. This test detects the high-risk HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68.

The cobas HPV Test 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=P100020

The SSED for P100020/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=P100020S017

The approval order statement for P100020/S017 is available on the CDRH website and is incorporated by reference here.
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P100020S017

The approval order statement for P100020/S025 is available on the CDRH website and is incorporated by reference here.
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P100020S025

The approval order statement for P100020/S049 is available on the CDRH website and is incorporated by reference here.
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P100020S049

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

The cobas HPV Test for use on the cobas 4800 System (cobas HPV Test) 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 or using a cervical broom and placed in SurePath Preservative Fluid.

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.

The cobas HPV Test 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 test labeling.

V. DEVICE DESCRIPTION

The cobas HPV Test is a qualitative in vitro test for the detection of Human Papillomavirus (HPV) in patient specimens. 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) HPV16 and HPV18 while concurrently detecting the rest of the high risk types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68).

The cobas HPV Test is based on two major processes: (1) automated specimen preparation to simultaneously extract HPV and cellular DNA; (2) PCR amplification of target DNA sequences using both HPV and beta-globin specific complementary primer pairs and real-time detection of cleaved fluorescent-labeled HPV and beta-globin specific oligonucleotide detection probes. The concurrent extraction, amplification and detection of beta-globin in the cobas HPV Test monitors the entire test process.

The Master Mix reagent for the cobas HPV Test contains primer pairs and probes specific for the 14 high-risk HPV types and beta-globin DNA. The detection of amplified DNA (amplicon) is performed during thermal cycling using oligonucleotide probes labeled with four different fluorescent dyes which are read on 4 different channels. 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 HPV 16, HPV18 and beta-globin signals are each detected with their own dedicated fluorescent dye.

The Test is run on the cobas 4800 system. The cobas 4800 system is a multi-instrument platform that will perform qualitative in vitro nucleic acid amplification tests from human specimens. The cobas 4800 system integrates automated total nucleic acid isolation directly from secondary sample tubes, PCR setup, and real-time PCR.

The cobas 4800 system software includes a validated two stage data analysis algorithm to determine the cycle threshold value (Ct) - the cycle number where the signal of the accumulating PCR product starts to grow exponentially in each channel as well as to check for the integrity of the signal. "Positive," "Negative," or "Invalid" result are determined for each sample in each channel based on predefined parameters and Ct cut offs for each channel. The ultimate result reported for each specimen or control is determined as a combination of results from all four detection channels according to predefined data analysis algorithm.

The result reporting architecture includes two options: (1) HR HPV only, and (2) HR HPV plus genotyping of 16 and 18. For the HR HPV only option, any positive signal from Channel I and/or channel 2 and/or channel 3 is reported as "HR HPV positive" and channel 4 (beta-globin signal) must be valid. For HR HPV plus genotyping option,

positivity is determined for each individual channel, thereby allowing the specific identification of HPV16 or HPV18 with the other HR HPV types detected collectively.

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 Results

Note: All assay and run validation is performed by the cobas 4800 software.
Note: A valid run may include both valid and invalid specimen results.
For a valid run, specimen results are interpreted as shown below:

Result Interpretation of the cobas® HPV Test for Presence of HPV DNA

cobas® HPV Test	**Result Report and Interpretation**
Requested Result "HPV High Risk Panel":	
POS HR HPV	**High Risk 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, 68.
NEG HR HPV	**High Risk 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	**High Risk HPV Invalid** Results are invalid. For PreservCyt® specimens, the original specimen should be retested no more than two times to obtain valid results. If the results are still invalid a new specimen should be obtained. For SurePath™ specimens, the original specimen should be retested if there is sufficient post-quot volume. If the results are still invalid a new specimen should be obtained.
Failed	**No Result for Specimen** Consult the **cobas®** 4800 System - User Assistance for instructions to review run flags and recommended actions. Original specimen should be re-tested to obtain valid result.
Requested Result "HPV High Risk Panel Plus Genotyping"	
POS Other HR HPV	**Other High Risk 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, 68.
NEG Other HR HPV	**Other High Risk HPV Negative*** HPV types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 DNA were undetectable or below the pre-set threshold.
Invalid Other HR HPV	**Invalid Other High Risk HPV** The result for Other HR HPV is Invalid. For PreservCyt® specimens, the original specimen should be retested no more than two times to obtain valid results. If the results are still invalid a new specimen should be obtained. For SurePath™ specimens, the original specimen should be retested if there is sufficient post-quot volume. If the results are still invalid a new specimen should be obtained.
POS HPV16	**HPV16 Positive** Specimen is positive for HPV type 16 DNA.
NEG HPV16	**HPV16 Negative*** HPV type 16 DNA was undetectable or below the pre-set threshold.
Invalid HPV16	**Invalid HPV16** The result for HPV16 is Invalid. For PreservCyt® specimens, the original specimen should be re-tested no more than two times to obtain valid results. If the results are still invalid a new specimen should be obtained. For SurePath™ specimens the original specimen should be retested if there is sufficient post-quot volume. If the results are still invalid a new specimen should be obtained.
POS HPV18	**HPV18 Positive** Specimen is positive for HPV type 18 DNA.
NEG HPV18	**HPV18 Negative*** HPV type 18 DNA was undetectable or below the pre-set threshold.

cobas® HPV Test	Result Report and Interpretation
Invalid HPV18	**Invalid HPV18** The result for HPV18 is Invalid. For PreservCyt® specimens, the original specimen should be re-tested no more than two times to obtain valid results. If the results are still invalid a new specimen should be obtained. For SurePath™ specimens the original specimen should be retested if there is sufficient post-quot volume. If the results are still invalid a new specimen should be obtained.
Failed	**No Result for Specimen** Consult the **cobas®** 4800 System - User Assistance for instructions to review run flags and recommended actions. Original specimen should be re-tested to obtain valid results.
*A negative result does not preclude the presence of HPV infection because results depend on adequate specimen collection, absence of inhibitors and sufficient DNA to be detected.	

Result Interpretation of the cobas HPV Test

Results	Interpretation for Patients with ASC-US cytology who are ≥ 21 years old	Interpretation for Patients with NILM cytology who are ≥ 30 years old
NEG Other HR HPV**, NEG HPV16, NEG HPV18	Very low likelihood of underlying ≥ CIN2.	Lowest likelihood of underlying ≥ CIN2.
POS Other HR HPV**, NEG HPV16, NEG HPV18	Increased likelihood that underlying ≥ CIN2 will be detected at colposcopy.	Low likelihood of underlying ≥ CIN2.
POS HPV16 and/or POS HPV18	Highest likelihood that underlying ≥ CIN2 will be detected at colposcopy[32, 33].	Increased likelihood of underlying ≥ CIN2.
*According to the 2006 consensus guidelines, HPV testing should not be performed on women younger than 21 years of age. **Other HR HPV DNA includes the following types: 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68.		

NOTE: HPV negative results are not intended to prevent women from proceeding to colposcopy.
NOTE: Negative results indicate HPV DNA concentrations are undetectable or below the pre-set threshold.
NOTE: Positive test results indicates the presence of any one or more of the high risk types, but since patients may be co-infected with low-risk types it does not rule out the presence of low-risk types in patients with mixed infections.
NOTE: Results of this test should only be interpreted in conjunction with information available from clinical evaluation of the patient and patient history.
NOTE: In addition to the results tabulated above, invalid results for one or more combinations are also possible and are reported out specifically for each channel.

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

VII. MARKETING HISTORY

This product has been marketed in Australia since the end of August, 2009. The product has been available for sale in the European Union since December 2009. The product was licensed in Canada in 2010. This device has been available in the U.S. since 2011. It has not been withdrawn from these markets for any reason.

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 test. 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 Test. 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 24 replicates were tested for each cell line level for each of two reagent lots. A total of six independent dilutions were prepared over a period of three days and tested using two instrument systems. 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)	200	24/24	38.1	100%
	100	20/24	39.3	83.3%
	50	14/24	39.8	58.3%
HeLa (HPV18)	80	24/24	37.9	100%
	40	17/24	38.9	70.8%
	20	12/24	39.4	50.0%

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 whole blood at 10% (v/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)	Yes, above 1.5%
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)	None
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 test 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 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 test.

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 specimens. The study protocol did not include any follow-up observations of enrolled participants unless required by the SOC.

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	26	530
2	511	2	21	488

C. Study Population Demographics and Baseline Parameters

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

Cohort 1

Age Category	Participants	Cervical HR HPV	Vaginal HR HPV
		Pos N (%)	Pos N (%)
25 - 29	199 (37.5%)	63 (31.6%)	69 (34.7%)
30 – 39	235 (44.3%)	61 (26.0%)	57 (24.2%)
40 – 49	87 (16.4%)	14 (16.1%)	19 (21.8%)
50+	9 (1.7%)	2 (22.2%)	2 (22.2%)
Total	530 (100%)	140 (26.4%)	147 (27.7%)

Cohort 2

Age Category	Participants	Cervical HR HPV Pos N (%)	Vaginal HR HPV Pos N (%)
25 - 29	191 (39.1%)	47 (24.6%)	54 (28.3%)
30 – 39	216 (44.3%)	54 (25.0%)	59 (27.3%)
40 – 49	63 (12.9%)	7 (11.1%)	12 (19.0%)
50+	18 (3.7%)	0 (0.0%)	1 (5.6%)
Total	488 (100%)	108 (22.1%)	126 (25.9%)

D. Safety and Effectiveness Results

1. Safety Results

With regards to safety, as an in vitro diagnostic test, the cobas HPV test 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 530 participants in cohort 1 with valid paired results and 488 participants in the 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 4.7% and 0.0%, respectively. For cohort 2, the rate of invalid results for the self-collected and clinician-collected specimens were 4.1% 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	21	2	5	28
	HR HPV "12 Other"	0	99	20	119
	HR HPV Negative	2	16	365	383
	Total	23	117	390	530
14 HR HPV PPA = 87.1% (122/140) (95% CI: 80.6% - 91.7%) HPV 16/18 PPA = 91.3% (21/23) (95% CI: 73.2% - 97.6%) 12 other HR HPV PPA = 84.6% (99/117) (95% CI: 77.0% - 90.0%) NPA = 93.6% (365/390) (95% CI: 90.7% - 95.6%)					

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	7	2	3	12
	HR HPV "12 Other"	0	82	32	114
	HR HPV Negative	1	16	345	362
	Total	8	100	380	488
14 HR HPV PPA = 84.3% (91/108) (95% CI: 76.2% - 89.9%) HPV 16/18 PPA = 87.5% (7/8) (95% CI: 52.9% - 97.8%) 12 other HR HPV PPA = 82.0% (82/100) (95% CI: 73.3% - 88.3%) NPA = 90.8% (345/380) (95% CI: 87.5% - 93.3%)					

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 test 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 test, 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 whole blood 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 test 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 test 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 test 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 test 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 test 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 test. 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 test 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 tests 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.