510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY TEMPLATE

A. 510(k) Number:

K043224

B. Purpose for Submission:

The APTIMA Combo 2 (AC2) assay is a nucleic acid amplification test (NAAT) intended for the qualitative detection and differentiation of ribosomal RNA from Chlamydia trachomatis (CT) and/or Neisseria gonorrhoeae (GC) in endocervical, male urethral and vaginal swab specimens and in female and male urine specimens. The assay originally received FDA clearance on May 21, 2001 (K032554). The current application is for the additional indication of testing specimens collected and processed with the Cytyc ThinPrep 2000 System. An ancillary kit called the "GEN-PROBE APTIMA Specimen Transfer Kit" is included in the current submission to facilitate specimen transport and processing.

C. Measurand:

Chlamydia trachomatis (CT) and/or *Neisseria gonorrhoeae* (GC) ribosomal RNA

D. Type of Test:

NAAT

E. Applicant:

Gen-Probe Incorporated

F. Proprietary and Established Names:

GEN-PROBE® APTIMA® Combo 2 Assay

G. Regulatory Information:

1. Regulation section:

   CT: 21 CFR 866.3120

   GC: 21 CFR 866.3390

2. Classification:

CT: Class I

GC: Class II

3. Product code:

   CT: MKZ

   GC: LSL

4. Panel:

   Microbiology (83)

H. Intended Use:

1. Intended use(s):

   AC2 Assay package insert:

   The APTIMA Combo 2 Assay is a target amplification nucleic acid probe test that utilizes target capture for the in vitro qualitative detection and differentiation of ribosomal RNA (rRNA) from Chlamydia trachomatis (CT) and/or Neisseria gonorrhoeae (GC) in clinician-collected endocervical, vaginal, and male urethral swab specimens, patient-collected vaginal swab specimens*, and female and male urine specimens. The assay is also intended for use with testing of gynecological specimens collected in the PreservCyt Solution and processed with the Cytyc ThinPrep 2000 System. The assay may be used to test specimens from symptomatic and asymptomatic individuals to aid in the diagnosis of gonococcal and/or chlamydial urogenital disease.

   *Patient-collected vaginal swab specimens are an option for screening women when a pelvic exam is not otherwise indicated. The vaginal swab specimen collection kit is not for home use.

   Ancillary Kit package insert:

   The GEN-PROBE® APTIMA® Specimen Transfer Kit is only for use with GEN-PROBE APTIMA assays for the detection of *Chlamydia trachomatis* and/or *Neisseria gonorrhoeae*. The GEN-PROBE APTIMA Specimen Transfer Kit allows for APTIMA Assay testing of gynecological specimens collected and processed by the Cytyc ThinPrep 200 Processor according to the instructions provided.

2. Indication(s) for use:

See intended use above

3. Special conditions for use statement(s):

   This device is for prescription use only.

4. Special instrument requirements:

   Gen-Probe Leader HC+ liminometer and Gen-Probe Target Capture System

I. Device Description:

The APTIMA Combo 2 (AC2) assay is a nucleic acid amplification test (NAAT).

See Test Principle below for more details.

J. Substantial Equivalence Information:

1. Predicate device name(s):
   APTMA Combo 2 Assay

2. Predicate 510(k) number(s):

   K003395

3. Comparison with predicate:

   Same device as current submission, but with added PreservCyt (PC) specimen indication. Collection device and media are different, as are specimen handling and storage instructions.

K. Standard/Guidance Document Referenced (if applicable):

Not Applicable

L. Test Principle:

The GEN-PROBE APTIMA Combo 2 Assay combines the technologies of target capture, Transcription-Mediated Amplification (TMA), and Dual Kinetic Assay (DKA). During target capture, rRNA molecules are isolated from specimens by capture oligomers on magnetic microparticles. After target capture, the specimens are ready for TMA. The GEN-PROBE APTIMA Combo 2 Assay reaction replicates a specific region of the 23S rRNA from C. trachomatis and a specific region of the 16S rRNA from N. gonorrhoeae via DNA intermediates. Detection of the rRNA amplicons is achieved using single-stranded chemiluminescent DNA probes, which are labeled with different acridinium ester molecules. The labeled DNA probes combine with amplicon to form stable RNA:DNA hybrids and light emitted from the labeled RNA:DNA hybrids is reported as Relative Light Units (RLU). In DKA, differences in the kinetic profiles of the CT and GC probes allow for the differentiation of signal. The chemiluminescent detection reaction for CT signal has the "flasher" kinetic type. The chemiluminescent detection reaction for the GC signal has the "glower" kinetic type. Assay results are determined by a cut-off based on the total RLU and the kinetic curve type.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

   a. Precision/Reproducibility:

   Precision testing was performed at three sites to obtain measures of repeatability and reproducibility. Reproducibility was established with a 12-member panel generated by spiking PreservCyt Solution with 0 to 2000 fg/assay of *C. trachomatis* and 0 to 5,000 fg/assay of *N. gonorrhoeae* rRNA

and aliquotting 1mL into the APTIMA Specimen Transfer Kit collection tube. Two (2) operators at each of the three sites performed one run per day on each of three days, totaling three valid runs per operator. Testing was performed using one assay kit lot. The results of this precision study are summarized below.

Reproducibility when testing PreservCyt liquid Pap clinical specimens containing target organism has not been determined.

Concentration (fg/assay)					Intra-Run		Inter-Run		Inter-Site		Inter-Operator	
CT	GC	N	Agreement	Mean RLU (x 1,000)	SD (x 1,000)	CV (%)	SD (x 1,000)	CV (%)	SD (x 1,000)	CV (%)	SD (x 1,000)	CV (%)
0	0	162	97.5%	9.7	31.6	N/A	3.4	N/A	6.4	N/A	4.7	N/A
0	5,000	54	96.3%	1296	146	11.3	54.8	4.2	0.0	0.0	0.0	0.0
2,000	0	54	100%	1140	54.1	4.7	79.8	7.0	101	8.9	2.4	0.2
2,000	5,000	54	100%	2345	79.6	3.4	78.0	3.3	94.7	4.0	37.9	1.6
0	250	54	100%	953	114	12.0	0.0	0.0	161	16.9	90.7	9.5
5	0	54	100%	971	58.3	6.0	71.7	7.4	22.8	2.4	85.0	8.8
1,000	2,500	54	100%	2294	114	5.0	88.9	3.9	153	6.7	0.0	0.0
100	250	54	98.1%	1911	139	7.3	130	6.8	348	18.2	39.7	2.1
5	5,000	54	100%	2136	113	5.3	130	6.1	98.8	4.6	166	7.8
2,000	250	54	96.3%	2044	138	6.7	169	8.3	360	17.6	26.9	1.3

RLU - Relative Light Units
SD = Standard Deviation
CV = Coefficient of Variation
N/A = Not applicable for negative panel members

b. *Linearity/assay reportable range:*

Not Applicable

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*

Not Applicable

d. *Detection limit:*

A study was performed that showed the AC2 Assay detected CT cells at least 4 fold below the analytical sensitivity claim (claim = 1 IFU/assay) for 3 replicates of each of 15 CT serovars tested in PC media. Likewise, 3 replicates of each of 20 GC clinical isolates were detected in PC media at 10 fold below the analytical sensitivity claim (claim = 50 cells/assay).

Table 5.5-10: Analytical Sensitivity for Detection of CT

Serovar	IFU/ Assay	Replicate 1		Replicate 2		Replicate 3	
		RLU	Result	RLU	Result	RLU	Result
A	10	1,006,000	CT+	1,019,000	CT+	964,000	CT+
	1.0	402,000	CT+	295,000	CT+	455,000	CT+
	0.1	55,000	CTe	82,000	CTe	41,000	CTe
	0.01	10,000	CT-	19,000	CT-	12,000	CT-
B	10	1,044,000	CT+	1,127,000	CT+	1,005,000	CT+
	1.0	607,000	CT+	725,000	CT+	724,000	CT+
	0.1	165,000	CT+	44,000	CTe	135,000	CT+
	0.01	68,000	CTe	27,000	CT-	18,000	CT-
Ba	10	1,159,000	CT+	1,201,000	CT+	1,275,000	CT+
	1.0	973,000	CT+	1,045,000	CT+	1,083,000	CT+
	0.1	699,000	CT+	826,000	CT+	783,000	CT+
	0.01	422,000	CT+	271,000	CT+	262,000	CT+
C	10	1,179,000	CT+	1,205,000	CT+	1,078,000	CT+
	1.0	740,000	CT+	716,000	CT+	576,000	CT+
	0.1	175,000	CT+	172,000	CT+	240,000	CT+
	0.01	7,000	CT-	17,000	CT-	40,000	CTe
D	10	989,000	CT+	1,005,000	CT+	993,000	CT+
	1.0	577,000	CT+	498,000	CT+	473,000	CT+
	0.1	48,000	CTe	56,000	CTe	91,000	CTe
	0.01	15,000	CT-	11,000	CT-	7,000	CT-
E	10	1,182,000	CT+	1,168,000	CT+	1,262,000	CT+
	1.0	1,134,000	CT+	1,150,000	CT+	1,204,000	CT+
	0.1	845,000	CT+	791,000	CT+	773,000	CT+
	0.01	442,000	CT+	403,000	CT+	268,000	CT+
F	10	1,167,000	CT+	1,179,000	CT+	1,169,000	CT+
	1.0	851,000	CT+	838,000	CT+	804,000	CT+
	0.1	241,000	CT+	6,000	CT-	19,000	CT-
	0.01	6,000	CT-	5,000	CT-	5,000	CT-
G	10	1,190,000	CT+	1,236,000	CT+	1,175,000	CT+
	1.0	1,018,000	CT+	1,030,000	CT+	979,000	CT+
	0.1	816,000	CT+	916,000	CT+	675,000	CT+
	0.01	71,000	CTe	412,000	CT+	454,000	CT+

e = Equivocal Result

Serovar	IFU/ Assay	Replicate 1		Replicate 2		Replicate 3	
		RLU	Result	RLU	Result	RLU	Result
H	10	1,156,000	CT+	1,120,000	CT+	1,111,000	CT+
	1.0	872,000	CT+	937,000	CT+	998,000	CT+
	0.1	795,000	CT+	733,000	CT+	657,000	CT+
	0.01	369,000	CT+	251,000	CT+	114,000	CT+
I	10	1,039,000	CT+	1,015,000	CT+	1,039,000	CT+
	1.0	1,025,000	CT+	992,000	CT+	896,000	CT+
	0.1	907,000	CT+	884,000	CT+	938,000	CT+
	0.01	899,000	CT+	924,000	CT+	928,000	CT+
J	10	1,159,000	CT+	1,221,000	CT+	1,297,000	CT+
	1.0	1,160,000	CT+	1,086,000	CT+	1,049,000	CT+
	0.1	802,000	CT+	805,000	CT+	788,000	CT+
	0.01	524,000	CT+	487,000	CT+	486,000	CT+
K	10	1,175,000	CT+	1,189,000	CT+	1,117,000	CT+
	1.0	886,000	CT+	844,000	CT+	909,000	CT+
	0.1	469,000	CT+	672,000	CT+	478,000	CT+
	0.01	5,000	CT-	5,000	CT-	7,000	CT-
L1	10	1,192,000	CT+	1,147,000	CT+	1,127,000	CT+
	1.0	947,000	CT+	935,000	CT+	942,000	CT+
	0.1	276,000	CT+	806,000	CT+	787,000	CT+
	0.01	504,000	CT+	334,000	CT+	294,000	CT+
L2	10	1,072,000	CT+	1,096,000	CT+	1,205,000	CT+
	1.0	979,000	CT+	859,000	CT+	901,000	CT+
	0.1	509,000	CT+	213,000	CT+	471,000	CT+
	0.01	11,000	CT-	5,000	CT-	230,000	CT+
L3	10	1,205,000	CT+	1,250,000	CT+	1,135,000	CT+
	1.0	999,000	CT+	967,000	CT+	951,000	CT+
	0.1	566,000	CT+	582,000	CT+	637,000	CT+
	0.01	196,000	CT+	9,000	CT-	111,000	CT+

e = Equivocal Result

Table 5.5-11: Additional Dilution Testing of CT Serovars A, B, D and F.

Serovar A					
IFU/Assay	Rep #	PreservCyt/STM		STM only	
		RLU	Results	RLU	Results
1.0	1	713,000	CT+	769,000	CT+
	2	632,000	CT+	675,000	CT+
	3	594,000	CT+	741,000	CT+
0.75	1	412,000	CT+	692,000	CT+
	2	287,000	CT+	674,000	CT+
	3	618,000	CT+	606,000	CT+
0.50	1	565,000	CT+	365,000	CT+
	2	344,000	CT+	109,000	CT+
	3	316,000	CT+	120,000	CT+
0.25	1	322,000	CT+	170,000	CT+
	2	272,000	CT+	279,000	CT+
	3	189,000	CT+	509,000	CT+
0.10	1	14,000	CT-	38,000	CTe
	2	43,000	CTe	44,000	CTe
	3	45,000	CTe	83,000	CTe
Serovar B					
IFU/Assay	Rep #	PreservCyt/STM		STM only	
		RLU	Results	RLU	Results
1.0	1	771,000	CT+	533,000	CT+
	2	754,000	CT+	572,000	CT+
	3	663,000	CT+	546,000	CT+
0.75	1	616,000	CT+	562,000	CT+
	2	576,000	CT+	539,000	CT+
	3	581,000	CT+	640,000	CT+
0.50	1	473,000	CT+	556,000	CT+
	2	454,000	CT+	620,000	CT+
	3	483,000	CT+	557,000	CT+
0.25	1	439,000	CT+	426,000	CT+
	2	514,000	CT+	360,000	CT+
	3	376,000	CT+	527,000	CT+
0.10	1	154,000	CT+	295,000	CT+
	2	216,000	CT+	175,000	CT+
	3	283,000	CT+	280,000	CT+

e = Equivocal Result

Table 5.5-11 (cont.). Additional Dilution Testing of CT Serovars A, B, D and F.

Serovar D					
IFU/Assay	Rep #	PreservCyt/STM		STM only	
		RLU	Results	RLU	Results
1.0	1	873,000	CT+	897,000	CT+
	2	904,000	CT+	928,000	CT+
	3	701,000	CT+	764,000	CT+
0.75	1	609,000	CT+	731,000	CT+
	2	422,000	CT+	649,000	CT+
	3	859,000	CT+	542,000	CT+
0.50	1	803,000	CT+	588,000	CT+
	2	628,000	CT+	465,000	CT+
	3	714,000	CT+	531,000	CT+
0.25	1	429,000	CT+	147,000	CT+
	2	366,000	CT+	250,000	CT+
	3	348,000	CT+	122,000	CT+
0.10	1	28,000	CT-	153,000	CT+
	2	92,000	CTe	170,000	CT+
	3	122,000	CT+	69,000	CTe
Serovar F					
IFU/Assay	Rep #	PreservCyt/STM		STM only	
		RLU	Results	RLU	Results
1.0	1	741,000	CT+	552,000	CT+
	2	863,000	CT+	133,000	CT+
	3	855,000	CT+	168,000	CT+
0.75	1	734,000	CT+	341,000	CT+
	2	716,000	CT+	168,000	CT+
	3	485,000	CT+	26,000	CT-
0.50	1	676,000	CT-	1,049,000	CT+
	2	310,000	CT+	911,000	CT+
	3	408,000	CT+	919,000	CT+
0.25	1	631,000	CT+	439,000	CT+
	2	561,000	CT+	725,000	CT+
	3	656,000	CT+	526,000	CT+
0.10	1	6,000	CT-	5,000	CT-
	2	7,000	CT-	6,000	CT-
	3	6,000	CT-	5,000	CT-

e = Equivocal Result

Table 5.5-12: Analytical Sensitivity for Detection of GC

GP Cl#	GC Cells Per Assay	Replicate 1 RLU	Result	Replicate 2 RLU	Result	Replicate 3 RLU	Result
760	500	1,195,000	GC+	1,181,000	GC+	1,051,000	GC+
	50	707,000	GC+	859,000	GC+	659,000	GC+
	5	326,000	GC+	420,000	GC+	466,000	GC+
	0.5	50,000	GC-	65,000	GC±	70,000	GC±
764	500	1,203,000	GC+	1,169,000	GC+	1,198,000	GC+
	50	1,073,000	GC+	1,049,000	GC+	1,120,000	GC+
	5	665,000	GC+	679,000	GC+	633,000	GC+
	0.5	79,000	GC±	107,000	GC±	45,000	GC-
772	500	1,277,000	GC+	1,255,000	GC+	1,234,000	GC+
	50	912,000	GC+	631,000	GC+	1,085,000	GC+
	5	532,000	GC+	394,000	GC+	652,000	GC+
	0.5	100,000	GC±	135,000	GC±	66,000	GC±
783	500	1,075,000	GC+	1,064,000	GC+	1,101,000	GC+
	50	983,000	GC+	938,000	GC+	963,000	GC+
	5	693,000	GC+	719,000	GC+	786,000	GC+
	0.5	226,000	GC+	237,000	GC+	283,000	GC+
787	500	1,146,000	GC+	1,046,000	GC+	1,093,000	GC+
	50	959,000	GC+	871,000	GC+	875,000	GC+
	5	295,000	GC+	397,000	GC+	396,000	GC+
	0.5	95,000	GC±	47,000	GC-	58,000	GC-
789	500	1,186,000	GC+	1,181,000	GC+	1,118,000	GC+
	50	954,000	GC+	1,014,000	GC+	941,000	GC+
	5	209,000	GC+	551,000	GC+	628,000	GC+
	0.5	264,000	GC+	129,000	GC±	93,000	GC±
790	500	1,041,000	GC+	1,011,000	GC+	1,034,000	GC+
	50	791,000	GC+	793,000	GC+	814,000	GC+
	5	365,000	GC+	313,000	GC+	275,000	GC+
	0.5	25,000	GC-	18,000	GC-	16,000	GC-
793	500	1,259,000	GC+	1,246,000	GC+	1,239,000	GC+
	50	1,182,000	GC+	1,150,000	GC+	1,139,000	GC+
	5	830,000	GC+	792,000	GC+	915,000	GC+
	0.5	343,000	GC+	386,000	GC+	349,000	GC+
794	500	1,192,000	GC+	1,117,000	GC+	1,237,000	GC+
	50	1,166,000	GC+	1,132,000	GC+	1,157,000	GC+
	5	797,000	GC+	159,000	GC+	706,000	GC+
	0.5	220,000	GC+	205,000	GC+	200,000	GC+
795	500	1,148,000	GC+	1,116,000	GC+	1,113,000	GC+
	50	923,000	GC+	1,038,000	GC+	1,053,000	GC+
	5	702,000	GC+	547,000	GC+	714,000	GC+
	0.5	177,000	GC+	93,000	GC+	158,000	GC+

GP Cl#	GC Cells Per Assay	Replicate 1 RLU	Replicate 1 Result	Replicate 2 RLU	Replicate 2 Result	Replicate 3 RLU	Replicate 3 Result
799	500	1,170,000	GC+	1,134,000	GC+	1,109,000	GC+
	50	976,000	GC+	950,000	GC+	992,000	GC+
	5	544,000	GC+	580,000	GC+	524,000	GC+
	0.5	62,000	GCe	54,000	GC-	103,000	GCe
800	500	1,231,000	GC+	1,221,000	GC+	1,213,000	GC+
	50	1,164,000	GC+	1,111,000	GC+	1,118,000	GC+
	5	903,000	GC+	931,000	GC+	900,000	GC+
	0.5	147,000	GCe	214,000	GC+	191,000	GC+
801	500	1,059,000	GC+	1,091,000	GC+	1,175,000	GC+
	50	1,002,000	GC+	1,025,000	GC+	974,000	GC+
	5	442,000	GC+	469,000	GC+	491,000	GC+
	0.5	62,000	GCe	69,000	GCe	40,000	GC-
802	500	1,156,000	GC+	1,187,000	GC+	1,168,000	GC+
	50	1,026,000	GC+	1,122,000	GC+	1,100,000	GC+
	5	709,000	GC+	622,000	GC+	323,000	GC+
	0.5	72,000	GCe	134,000	GCe	153,000	GC+
806	500	1,145,000	GC+	1,088,000	GC+	1,010,000	GC+
	50	781,000	GC+	851,000	GC+	822,000	GC+
	5	255,000	GC+	247,000	GC+	178,000	GC+
	0.5	61,000	GCe	31,000	GC-	39,000	GC-
813	500	1,112,000	GC+	1,134,000	GC-	1,163,000	GC+
	50	1,006,000	GC+	1,030,000	GC+	1,108,000	GC+
	5	669,000	GC+	688,000	GC+	608,000	GC+
	0.5	141,000	GCe	135,000	GCe	176,000	GC+
827	500	1,192,000	GC+	1,089,000	GC+	1,250,000	GC+
	50	1,168,000	GC+	1,192,000	GC+	1,133,000	GC+
	5	744,000	GC+	841,000	GC+	712,000	GC+
	0.5	178,000	GC+	245,000	GC+	202,000	GC+
3043	500	1,235,000	GC+	1,238,000	GC+	1,232,000	GC+
	50	1,090,000	GC+	1,036,000	GC+	1,125,000	GC+
	5	292,000	GC+	591,000	GC+	493,000	GC+
	0.5	78,000	GCe	99,000	GCe	73,000	GCe
3045	500	1,184,000	GC+	1,110,000	GC+	1,211,000	GC+
	50	1,116,000	GC+	1,077,000	GC+	978,000	GC+
	5	641,000	GC+	808,000	GC+	513,000	GC+
	0.5	110,000	GCe	111,000	GCe	151,000	GC+
3047	500	1,189,000	GC+	1,174,000	GC+	1,163,000	GC+
	50	1,071,000	GC+	1,148,000	GC+	1,182,000	GC+
	5	880,000	GC+	896,000	GC+	794,000	GC+
	0.5	70,000	GCe	207,000	GC+	177,000	GC+

e = Equivocal Result

e. Analytical specificity:

The Chlamydia and Neisseria species were used to evaluate the analytical specificity of the AC2 Assay. A total of 50 culture isolates were tested in the liquid Pap media. None of the 50 culture isolates produced a positive result in the AC2 Assay. See results below:

Table 5.5-13: Specificity of the AC2 Assay

PHYLOGENETIC CROSS-SECTION	GP No.	ATCC No.	Concentration Tested/Assay	Rep #	Results (RLU)
Chlamydia psittaci	1557	VR601	7.9×10^4 cells	1 2	5,000 4,000
Chlamydia psittaci	768	VR629	1×10^4 $CELD_{50}$/0.2 ml	1 2	4,000 5,000
Chlamydia pneumoniae	1404	VR1360	4.0×10^7 cells	1 2	5,000 6,000
Neisseria elongata	CI1502	49377	1.2×10^9 cells	1 2	6,000 6,000
Neisseria elongata	CI1503	49378	1.2×10^8 cells	1 2	5,000 5,000
Neisseria elongata	CI1504	49379	1.8×10^8 cells	1 2	9,000 10,000
Neisseria flava	1558	14221	2.5×10^9 cells	1 2	4,000 4,000
Neisseria mucosa	190	19696	2.4×10^8 cells	1 2	5,000 5,000
Neisseria mucosa	791	25999	1.3×10^8 cells	1 2	5,000 4,000
Neisseria perflava	1559	10555	1.0×10^8 cells	1 2	6,000 4,000
Neisseria sicca	272	9913	5.9×10^8 cells	1 2	5,000 4,000
Neisseria sicca	762	29193	7.2×10^7 cells	1 2	4,000 4,000
Neisseria subflava	CI3113	NA	4.5×10^7 cells	1 2	4,000 4,000
Neisseria subflava	NH1	NA	2.2×10^7 cells	1 2	4,000 3,000
Neisseria subflava	NH5	NA	2.4×10^7 cells	1 2	3,000 4,000
Neisseria subflava	NH6	NA	2.7×10^8 cells	1 2	4,000 4,000
Neisseria subflava	NH7	NA	1.2×10^9 cells	1 2	4,000 5,000
Neisseria subflava	NH8	NA	4.7×10^8 cells	1 2	6,000 4,000
Neisseria subflava	NH11	NA	1.0×10^9 cells	1 2	5,000 5,000
Neisseria subflava	NH13	NA	3.0×10^7 cells	1 2	6,000 6,000

PHYLOGENETIC CROSS-SECTION	GP No.	ATCC No.	Concentration Tested/Assay	Rep #	Results (RLU)
Neisseria subflava	NH14	NA	4.5 x 10^7 cells	1 2	6,000 5,000
Neisseria subflava	NH15	NA	8.7 x 10^7 cells	1 2	4,000 4,000
Neisseria subflava	NH17	NA	1.1 x 10^9 cells	1 2	3,000 4,000
Neisseria subflava	NH18	NA	5.7 x 10^7 cells	1 2	5,000 5,000
Neisseria subflava	NH20	NA	2.1 x 10^8 cells	1 2	6,000 5,000
Neisseria cinerea	761	14685	1.6 x 10^9 cells	1 2	8,000 8,000
Neisseria cinerea	CI3051	NA	2.9 x 10^8 cells	1 2	8,000 8,000
Neisseria cinerea	CI4543	NA	1.3 x 10^8 cells	1 2	9,000 10,000
Neisseria cinerea	CI4546	NA	4.9 x 10^8 cells	1 2	7,000 7,000
Neisseria dentrificans	763	14686	3.0 x 10^8 cells	1 2	5,000 4,000
Neisseria lactamica	760	23970	1.1 x 10^9 cells	1 2	6,000 6,000
Neisseria lactamica	CI3013	NA	9.5 x 10^8 cells	1 2	5,000 5,000
Neisseria lactamica	CI3018	NA	1.5 x 10^8 cells	1 2	5,000 4,000
Neisseria lactamica	CI3021	NA	5.0 x 10^9 cells	1 2	4,000 14,000
Neisseria lactamica	CI3022	NA	9.4 x 10^9 cells	1 2	5,000 4,000
Neisseria lactamica	CI3049	NA	2.3 x 10^{10} cells	1 2	5,000 4,000
Neisseria lactamica	CI3065	NA	1.5 x 10^{10} cells	1 2	4,000 5,000
Neisseria lactamica	CI3067	NA	2.9 x 10^{10} cells	1 2	4,000 4,000
Neisseria lactamica	CI834	NA	6.0 x 10^9 cells	1 2	6,000 5,000
N. meningitidis Serogroup A	755	13077	4.0 x 10^{10} cells	1 2	9,000 8,000
N. meningitidis Serogroup B	756	13090	3.1 x 10^8 cells	1 2	6,000 6,000

PHYLOGENETIC CROSS-SECTION	GP No.	ATCC No.	Concentration Tested/Assay	Rep #	Results (RLU)
N. meningitidis Serogroup C	757	13102	5.0 x 10^8 cells	1 2	8,000 8,000
N. meningitidis Serogroup C	1388	13109	2.9 x 10^{11} cells	1 2	5,000 4,000
N. meningitidis Serogroup C	1389	13100	8.0 x 10^{10} cells	1 2	5,000 4,000
N. meningitidis Serogroup C	1390	13112	2.7 x 10^8 cells	1 2	10,000 7,000
N. meningitidis Serogroup D	401	13113	1.7 x 10^{11} cells	1 2	8,000 7,000
N. meningitidis Serogroup Y	787	35561	3.0 x 10^{10} cells	1 2	8,000 9,000
N. meningitidis Serogroup W135	1387	43744	1.6 x 10^9 cells	1 2	10,000 10,000
Neisseria polysaccharea	1489	43768	3.0 x 10^9 cells	1 2	12,000 12,000

f. Assay cut-off:

Not Applicable

2. <u>Comparison studies:</u>

a. Method comparison with predicate device:

Not Applicable

3. Clinical studies:

A prospective multi-center clinical study was conducted to evaluate the use of the PreservCyt Solution (a component of the ThinPrep 2000 System) as an alternative medium for gynecological specimens for the detection of Chlamydia trachomatis and Neisseria gonorrhoeae. One thousand six hundred forty-seven (1,647) symptomatic and asymptomatic female subjects attending OB/GYN, family planning, public health, women's and STD clinics were evaluated in the clinical study. Of the 1,647 evaluable subjects, 1,288 were asymptomatic subjects and 359 were symptomatic subjects. Subjects were enrolled from sites with CT prevalence that ranged from 3.2 to 14.0% and GC prevalence that ranged from 0 to 5.0%. Two specimens were collected from each eligible subject: one PreservCyt Solution specimen and one endocervical swab. PreservCyt Solution specimens were processed in accordance with the ThinPrep 2000 Processor Operator's Manual and APTIMA Specimen Transfer Kit Package Insert. After processing the PreservCyt Solution specimen with the ThinPrep 2000 Processor, the specimen was transferred into the APTIMA Specimen Transfer Kit for testing with the APTIMA Combo 2 Assay. The PreservCyt liquid Pap specimens and endocervical swab specimens were tested with the APTIMA Combo 2 Assay.

Sensitivity and specificity for PreservCyt liquid Pap specimens were calculated by comparing results to a patient infected status algorithm. In the algorithm, the designation of a subject as being infected or non-infected with C. trachomatis or N.gonorrhoeae was based on endocervical swab specimen results from two commercially-available NAATs. For C. trachomatis, the reference NAATs included the APTIMA Combo 2 Assay and the APTIMA CT Assay. For N. gonorrhoeae, the reference NAATs included the APTIMA Combo 2 Assay and the APTIMA GC Assay. Positive results from both reference NAATs were required to establish an infected patient. A non-infected patient was established if the results from the two reference NAATs disagreed or were negative.

Sensitivity and specificity for C. trachomatis in PreservCyt liquid Pap specimens tested in the APTIMA Combo 2 Assay, by symptom status and overall, is presented in Table 5c. For C. trachomatis, overall sensitivity was 96.7% (87/90). In symptomatic and asymptomatic subjects, sensitivity was 96.7% (29/30) and 96.7% (58/60), respectively. Overall specificity for C. trachomatis PreservCyt liquid Pap specimens was 99.2% (1545/1557). In symptomatic and asymptomatic subjects, specificity was 98.5% (324/329) and 99.4% (1221/1228), respectively. Table 6c shows the APTIMA Combo 2 Assay sensitivity and specificity values for C. trachomatis in PreservCyt

liquid Pap specimens by clinical site and overall. For C. trachomatis, the sensitivity ranged from 92.9% to 100%. The specificity ranged from 97.7% to 100%. Sensitivity and specificity for N. gonorrhoeae in PreservCyt liquid Pap specimens tested in the APTIMA Combo 2 Assay, by symptom status and overall, is presented in Table 9c. For N. gonorrhoeae, overall sensitivity was 92.3% (12/13). In symptomatic and asymptomatic subjects, sensitivity was 100% (7/7) and 83.3% (5/6), respectively. Overall specificity for N. gonorrhoeae PreservCyt liquid Pap specimens was 99.8% (1630/1633). In symptomatic and asymptomatic subjects, specificity was 100% (352/352) and 99.8% (1278/1281), respectively. Table 10c shows the APTIMA Combo 2 Assay sensitivity and specificity values for N. gonorrhoeae in PreservCyt liquid Pap specimens by clinical site and overall. For N. gonorrhoeae, the sensitivity ranged from 80.0% to 100%. Specificity ranged from 99.0% to 100%

Table 7c. *C. trachomatis* PreservCyt Liquid Pap Specimen Analysis for Female Patient Infected Status

	Endocervical Swab		Symptom Status	
Patient Infected Status	APTIMA Combo 2 Assay	APTIMA CT Assay	Symptomatic	Asymptomatic
Infected	+	+	30	60
Non-Infected	-	+	4	12
Non-Infected	+	-	3	2
Non-Infected	-	-	322	1214
Total			359	1288

Table 5c. *C. trachomatis* Sensitivity and Specificity: APTIMA Combo 2 Assay PreservCyt Specimens vs. Patient Infected Status

Symptom Status	AC2/CT ThinPrep Result	+/+	+/-	-/+	-/-	Sensitivity (95% C.I.)	Specificity (95% C.I.)
Asymptomatic	Positive	58	1	0	6		
	Negative	2	1	12	1208	96.7% (88.5 - 99.6)	99.4% (98.8 - 99.8)
	Total	60	2	12	1214		
Symptomatic	Positive	29	0	0	5		
	Negative	1	3	4	317	96.7% (82.8 - 99.9)	98.5% (96.5 - 99.5)
	Total	30	3	4	322		
All	Positive	87	1	0	11		
	Negative	3	4	16	1525	96.7% (90.6 - 99.3)	99.2% (98.7 - 99.6)
	Total	90	5	16	1536		

+/+ = Positive Endocervical Swab Specimen Result in the AC2 Assay / Positive Endocervical Swab Specimen Result in the ACT Assay
+/- = Positive Endocervical Swab Specimen Result in the AC2 Assay / Negative Endocervical Swab Specimen Result in the ACT Assay
-/+ = Negative Endocervical Swab Specimen Result in the AC2 Assay / Positive Endocervical Swab Specimen Result in the ACT Assay
-/- = Negative Endocervical Swab Specimen Result in the AC2 Assay / Negative Endocervical Swab Specimen Result in the ACT Assay

Table 6c. *C. trachomatis* Performance by Clinical Site: APTIMA Combo 2 Assay PreservCyt Specimens vs. Patient Infected Status

Site	AC2/CT ThinPrep Result	+/+	+/-	-/+	-/-	Prev (%)	Sensitivity (95% C.I.)	Specificity (95% C.I.)	PPV (%)	NPV (%)
1	Positive	14	0	0	2					
	Negative	0	0	1	83	14.0	100% (76.8 - 100)	97.7% (91.9 - 99.7)	87.5	100
	Total	14	0	1	85					
2	Positive	4	0	0	0					
	Negative	0	0	2	118	3.2	100% (39.8 - 100)	100% (97.0 - 100)	100	100
	Total	4	0	2	118					
3	Positive	29	0	0	2					
	Negative	2	0	2	440	6.5	93.5% (78.6 - 99.2)	99.5% (98.4 - 99.9)	93.5	99.5
	Total	31	0	2	442					
4	Positive	8	1	0	4					
	Negative	0	2	1	271	2.8	100% (63.1 - 100)	98.2% (95.9 - 99.4)	61.5	100
	Total	8	3	1	275					
5	Positive	13	0	0	2					
	Negative	1	1	4	276	4.7	92.9% (66.1 - 99.8)	99.3% (97.5 - 99.9)	86.7	99.6
	Total	14	1	4	278					
6	Positive	19	0	0	1					
	Negative	0	1	6	337	5.2	100% (82.4 - 100)	99.7% (98.4 - 100)	95.0	100
	Total	19	1	6	338					
All	Positive	87	1	0	11					
	Negative	3	4	16	1525	5.5	96.7% (90.6 - 99.3)	99.2% (98.7 - 99.6)	87.9	99.8
	Total	90	5	16	1536					

+/+ = Positive Endocervical Swab Specimen Result in the AC2 Assay / Positive Endocervical Swab Specimen Result in the ACT Assay
+/- = Positive Endocervical Swab Specimen Result in the AC2 Assay / Negative Endocervical Swab Specimen Result in the ACT Assay
-/+ = Negative Endocervical Swab Specimen Result in the AC2 Assay / Positive Endocervical Swab Specimen Result in the ACT Assay
-/- = Negative Endocervical Swab Specimen Result in the AC2 Assay / Negative Endocervical Swab Specimen Result in the ACT Assay

Table 11c. *N. gonorrhoea* PreservCyt Liquid Pap Specimen Analysis for Female Patient Infected Status

	Endocervical Swab		Symptom Status	
Patient Infected Status	APTIMA Combo 2 Assay	APTIMA GC Assay	Symptomatic	Asymptomatic
Infected	+	+	7	6
Non-Infected	=	+	0	1
Non-Infected	-	+	0	5
Non-Infected	-	-	352	1276
Total			359	1288

The equal symbol ("=") represents an equivocal result.

Table 9c. *N. gonorrhoeae* Sensitivity and Specificity: APTIMA Combo 2 Assay PreservCyt Specimens vs. Patient Infected Status

Symptom Status	AC2/GC ThinPrep Result	+/+	+/-	-/+	-/-	Sensitivity (95% C.I.)	Specificity (95% C.I.)
Asymptomatic	Positive	5	0	0	3		
	Negative	1	0	5	1273	83.3% (35.9 - 99.6)	99.8% (99.3 - 100)
	Total	6	0	5	1276		
Symptomatic	Positive	7	0	0	0		
	Negative	0	0	0	352	100% (59.0 - 100)	100% (99.0 - 100)
	Total	7	0	0	352		
All	Positive	12	0	0	3		
	Negative	1	0	5	1625	92.3% (64.0 - 99.8)	99.8% (99.5 - 100)
	Total	13	0	5	1628		

+/+ = Positive Endocervical Swab Specimen Result in the AC2 Assay / Positive Endocervical Swab Specimen Result in the AGC Assay
+/- = Positive Endocervical Swab Specimen Result in the AC2 Assay / Negative Endocervical Swab Specimen Result in the AGC Assay
-/+ = Negative Endocervical Swab Specimen Result in the AC2 Assay / Positive Endocervical Swab Specimen Result in the AGC Assay
-/- = Negative Endocervical Swab Specimen Result in the AC2 Assay / Negative Endocervical Swab Specimen Result in the AGC Assay

Table 10c. *N. gonorrhoeae* Performance by Clinical Site: APTIMA Combo 2 Assay PreservCyt Specimens vs. Patient Infected Status

Site	AC2/GC ThinPrep Result	+/+	+/-	-/+	-/-	Prev (%)	Sensitivity (95% C.I.)	Specificity (95% C.I.)	PPV (%)	NPV (%)
1	Positive	5	0	0	0	5.0				
	Negative	0	0	0	95		100% (47.8 - 100)	100% (96.2 - 100)	100	100
	Total	5	0	0	95					
2	Positive	1	0	0	0					
	Negative	0	0	0	123	0.8	100% (2.5 - 100)	100% (97.0 - 100)	100	100
	Total	1	0	0	123					
3	Positive	4	0	0	0					
	Negative	1	0	0	470	1.1	80.0% (28.4 - 99.5)	100% (99.2 - 100)	100	99.8
	Total	5	0	0	470					
4	Positive	1	0	0	0					
	Negative	0	0	3	283	0.3	100% (2.5 - 100)	100% (98.7 - 100)	100	100
	Total	1	0	3	283					
5	Positive	0	0	0	3					
	Negative	0	0	0	294	0.0	N/A	99.0% (97.1 - 99.8)	0.0	100
	Total	0	0	0	297					
6	Positive	1	0	0	0					
	Negative	0	0	2	360	0.3	100% (2.5 - 100)	100% (99.0 - 100)	100	100
	Total	1	0	2	360					
All	Positive	12	0	0	3					
	Negative	1	0	5	1625	0.8	92.3% (64.0 - 99.8)	99.8% (99.5 - 100)	80.0	99.9
	Total	13	0	5	1628					

+/+ = Positive Endocervical Swab Specimen Result in the AC2 Assay / Positive Endocervical Swab Specimen Result in the AGC Assay
+/- = Positive Endocervical Swab Specimen Result in the AC2 Assay / Negative Endocervical Swab Specimen Result in the AGC Assay
-/+ = Negative Endocervical Swab Specimen Result in the AC2 Assay / Positive Endocervical Swab Specimen Result in the AGC Assay
-/- = Negative Endocervical Swab Specimen Result in the AC2 Assay / Negative Endocervical Swab Specimen Result in the AGC Assay

4. Clinical cut-off**:**

   Not Applicable

5. Expected values/Reference range:

The prevalence of C. trachomatis and/or N. gonorrhoeae disease in patient populations depends on risk factors such as age, gender, the presence of symptoms,

the type of clinic, and the test method. A summary of the prevalence of *C. trachomatis* and *N. gonorrhoeae* as determined by the APTIMA Combo 2 Assay results on PreservCyt liquid Pap specimens is shown below by clinical site and overall.

Table 1c. Prevalence of *C. trachomatis* and/or *N. gonorrhoeae* Disease by Clinical Site: PreservCyt liquid Pap Specimen

	PreservCyt liquid Pap % Prevalence (# positive/# tested)		
Site	**CT+/GC+**	**CT+/GC-**	**CT-/GC+**
1	3.0 (3/100)	13.0 (13/100)	2.0 (2/100)
2	0 (0/124)	3.2 (4/124)	0.8 (1/124)
3	0.4 (2/475)	6.1 (29/475)	0.4 (2/475)
4	0.4 (1/287)	4.2 (12/287)	0 (0/287)
5	0 (0/297)	5.1 (15/297)	1.0 (3/297)
6	0 (0/364)	5.5 (20/364)	0.6 (2/364)
ALL	0.4 (6/1647)	5.6 (93/1647)	0.6 (10/1647)

Note: The CT and GC prevalence were calculated using the APTIMA Combo 2 Assay results of PreservCyt liquid Pap specimen.

N. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

O. Conclusion:

1. The submitted information in this premarket notification is complete and supports a substantial equivalence decision.