EVALUATION OF AUTOMATIC CLASS III DESIGNATION FOR THE AGAR PLATE ASSESSMENT SYSTEM (APAS) COMPACT

DECISION MEMORANDUM

A. 510(k) Number:

DEN150059

B. Purpose for Submission:

De novo request for evaluation of automatic class III designation for the Agar Plate Assessment System (APAS) Compact

C. Measurand:

Digital images of microbial colonies cultured on blood and MacConkey agar plates

D. Type of Test:

The APAS Compact when using its Urine Analysis Module (the "APAS Compact" or the "APAS Compact with Urine Analysis Module") is an *in vitro* diagnostic test system for automated assessment and enumeration of microbial colonies on solid culture media. The system is for use on urine cultures from suspected cases of urinary tract infection (UTI).

E. Applicant:

Clever Culture Systems AG

F. Proprietary and Established Names:

APAS Compact

G. Regulatory Information:

1. Regulation section:

   21 CFR 866.2190 Automated image assessment system for microbial colonies on solid culture media

2. Classification:

   Class II

3. Product code:

   PPU

4. Panel:

   83 - Microbiology

H. Indications for Use:

1. Indication(s) for Use:

   The APAS Compact is an *in vitro* diagnostic system comprised of an instrument for automated imaging of agar culture plates and a software analysis module for the following use:

   The APAS Compact, when using its urine analysis module, automates urine culture plate imaging and interpretation to detect the presence or absence of microbial growth on sheep blood and MacConkey agar culture plates that are inoculated with a 1µL sample volume. The APAS Compact, when using its urine analysis module, provides a semi-quantitative assessment of colony counts that are used as an aid in the diagnosis of urinary tract infection. All urine culture plates that are identified as positive for growth by the APAS Compact, when using its urine analysis module, must be reviewed by a trained microbiologist.

2. Special conditions for use statement(s):

   For prescription use only.

   The performance of APAS Compact with Urine Analysis Module has not been evaluated with urine samples from pregnant women. The APAS Compact with Urine Analysis Module will detect colonies of GBS if they are present but should not be used for the primary screening for Group B *Streptococcus* (GBS) carriers. Follow recommended guidelines for identification of pregnant women who are colonized with GBS.[1]

   The performance of the APAS Compact with Urine Analysis Module has not been evaluated with urine samples from suspected cases of complicated urinary tract infection e.g., those with underlying urinary tract pathology, suspected cases of persistent urinary tract infection, urine collected by invasive procedures or urine samples from immunocompromised subjects.

   Slow growing organisms such as *Corynebacterium* spp. and *Gardnerella vaginalis* may not exhibit detectable growth within 18-22 hours. If infection with a slow growing species is suspected, extension of the incubation time may be required, followed by manual interpretation of the culture result. APAS Compact with Urine Analysis Module should not be used to interpret cultures incubated for greater than 22 hours.

   The APAS Compact with Urine Analysis Module is qualified for use with the following culture plates manufactured by Remel: Tryptic Soy Sheep Blood Agar and MacConkey Agar with Crystal Violet.

[1] CDC Guidelines, 2010: Prevention of perinatal Group B Streptococcal disease.

3. Special instrument requirements:

APAS Compact

I. Device Description:

The APAS Compact with Urine Analysis Module is an instrumented system that is designed for screening of urine culture plates for the presence of microbial growth. The device comprises an imaging station for capture of digital images of the culture plates, together with software for analysis of the images, the determination and enumeration of microbial growth and reporting of results. A list of the major sub-components of the APAS Compact is depicted in **Table 1**. The Urine Analysis Module software is compatible with the following types of culture media:

Tryptic Soy Sheep Blood Agar
MacConkey Agar with Crystal Violet

Table 1. Sub-components of the APAS Compact

Component	Function
Imaging Station	Light Emitting Diode (LED) illumination of culture plates and image capture using a Charge Coupled Device (CCD) camera
APAS Controller Personal Computer (PC)	Image capture, storage and analysis
Urine Analysis Module Software	Installed on the APAS Controller PC to provide the configuration and instructions for image capture and analysis
Instrument Controller Software	User interface for operation of the APAS Compact
LIMS Interface Software	Installed on the Instrument Controller PC and used to import other diagnostic information, such as microscopy or chemistry results, and provide context for interpretation of urine culture results. Imported information may be applied to the system: "LIMS Force Flag": automatically forces an APAS result to "Review" irrespective of the growth characteristics observed "LIMS Complementary Test Flag": automatically changes a "Negative" designation to "Review" based on user defined rules applied to additional diagnostic information
Color Calibration Tool	Multicolored disk for calibration of the system optics

The imaging station comprises a fixed CCD camera, top and bottom LED illumination for the culture plates and a plate handling mechanism, all of which are housed in a light-sealed chassis. The Instrument Controller PC provides the user interface and sends instructions to the APAS Controller PC which in turn controls the imaging station.

The plate handling mechanism of the imaging station comprises a manual lever that allows

the operator to load a single culture plate into the system and position it for imaging. The operator then initiates image capture using the Instrument Controller PC. Once an image is taken by the camera it is sent to the APAS Controller PC for assessment and storage. APAS Compact reports are viewed on a separate computer through a dedicated user interface.

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

IEC 61010-1: Safety requirements for electrical equipment for measurement, control and laboratory use - Part 1: General requirements, 3rd Edition.

IEC 61326-2-6: Electrical equipment for measurement, control and laboratory use - EMC Requirements - Part 2-6: Particular Requirements – *In vitro* diagnostic (IVD) medical Equipment, 2nd Edition.

IEC 62304 Medical device software - software lifecycle processes, 1st Edition.

ISO 14971 Medical devices - Application of Risk Management to Medical Devices, 2007.

CISPR 11 Industrial, scientific and medical equipment - radio frequency disturbance characteristics - Limits and methods of measurement, Version 5.1.

K. Test Principle:

The APAS Compact with Urine Analysis Module is designed for the assessment of microbial colonies on urine culture plates. The device comprises an imaging station for capture of images of the culture plates, together with software for analysis of the images, the assessment and enumeration of microbial colonies and result designation. Plates with growth are designated as either "Positive" or "Review" depending on the number of colonies present and their morphologic characteristics. All samples that exhibit growth therefore require follow up according to standard laboratory practice by a trained microbiologist. Plates that are designated by the APAS Compact to have no growth may be discarded without further review.

The APAS Compact with Urine Analysis Module is indicated for screening paired sheep blood and MacConkey agar plates that are each inoculated with 1µl of urine and which are incubated at 35°C ± 2°C for 18 to 22 hours. For each urine sample, both culture plates must be processed on the APAS Compact. The system takes digital images of each plate which are analyzed automatically to determine the number of colonies present and their associated morphologies. For each plate, the APAS Compact performs the following tasks:

a) Differentiates between areas of growth (colonies) and no growth (e.g., agar, labels, handwriting);
b) Differentiates areas that are required for interpretation of colony morphology (e.g., α- and β-hemolysis);
c) Assigns to each area of growth a code that corresponds to a morphology type;
d) Estimates the number of colonies present, converts this number to an organism concentration in the original urine sample and reports it in terms of colony forming units per milliliter (CFU/mL).

The interpretation of the growth on a pair of plates follows a decision tree whereby the two plate reports are combined and a designation is made for the sample.

The colony morphologies reported by the APAS Compact with Urine Analysis Module are shown in **Table 2** for sheep blood agar and **Table 3** for MacConkey agar. A summary of the result logic used for automated interpretation of the colony counts and morphology is shown in **Table 4**. A "significant organism" at 10^3 CFU/mL on the plate will trigger designation of that plate as "Positive," as opposed to "Review." Plates that are designated as "Positive" or "Review" undergo further evaluation by a clinical microbiologist.

Table 2. Colony morphologies on sheep blood agar identified by APAS Compact with Urine Analysis Module

Morphology Name	Description
Coliform	Gram-negative and coliform-like colonies
Cream-white	*Staphylococcus* and related species
Granular	Granular morphologies (e.g., *Pseudomonas* spp.)
Small	*Enterococcus* spp. and related species
Small α-hemolytic	Small colonies with α-hemolysis or very small colonies
Small β-hemolytic	Small colonies with β-hemolysis
Swarming organism	*Proteus* spp. and related, high-motility species

Table 3. Colony morphologies on MacConkey agar identified by APAS Compact with Urine Analysis Module

Morphology Name	Description
Lactose fermenter	Pink/red colonies
Non-fermenter	Colonies without red/pink pigment
Non-fermenter with green pigment	*Pseudomonas* spp.
Red pigmented colonies	Pigmented *Serratia marcescens*

Table 4. Result interpretation for APAS Compact with Urine Analysis Module

Colony Count (CFU/mL)	Morphology	APAS Compact Designation
Not Applicable	Swarming organism	Positive
$\geq 10^4$	Any	
10^3	Significant organism [1]	
10^3	No significant organism	Review
0	Not Applicable	Negative

[1] Defined as growth of coliform or small colonies with β-hemolysis on blood agar or lactose fermenting colonies on MacConkey agar

L. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

The reproducibility of colony counts performed by the APAS Compact with Urine Analysis Module was evaluated on different instruments over multiple runs. Testing was performed using $\log_{10}$-fold dilutions of 0.5 McFarland standard suspensions of representative uropathogenic species that produced from 0 to >100 colonies per plate. Each dilution was plated in triplicate and incubated for 18 hours at 35°C. Images of each plate were taken at 5 different orientations (0, 60, 120, 180 and 270°) on each of 3 APAS Compact instruments. The mean and standard deviation of the resulting colony counts was determined for each dilution on each instrument and overall (**Tables 5** and **6**). The results demonstrated acceptable reproducibility of colony counts between instruments and rotations of the same plate.

Table 5. Reproducibility of colony counts on blood agar obtained by the APAS Compact with Urine Analysis Module

Species	Dilution [1]	Replicate	Instrument 1		Instrument 2		Instrument 3		Overall			
			Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV
E. coli	3	1	76.2	1.9	83.2	4.4	74.0	2.1	77.8	6.0	78.3	7.0
		2	85.8	3.6	82.8	4.2	82.6	1.8	83.7	3.6		
		3	72.8	2.5	73.6	2.6	73.4	3.7	73.3	2.8		
	4	1	8.6	10.3	8.2	5.5	8.2	5.5	8.3	7.5	18.6	39.2
		2	23.2	1.9	23.8	1.9	23.0	0.0	23.3	2.1		
		3	23.8	1.9	23.8	6.2	24.4	2.3	24.0	3.9		
	5	1	5.6	9.8	5.6	9.8	5.6	9.8	5.6	9.1	3.2	75.0
		2	4.0	0.0	4.0	0.0	4.0	0.0	4.0	0.0		
		3	0.0	NA	0.0	NA	0.0	NA	0.0	NA		
E. coli/S. agalactiae	3	1	207.8	5.54	242.4	6.16	165.0	5.7	205.1	16.9	202.2	38.0
		2	141.8	6.09	135.6	10.18	108.6	4.3	128.7	13.6		
		3	345.6	10.60	297.6	4.23	175.6	4.0	272.9	28.2		
	4	1	14.4	6.18	16.4	13.35	15.2	7.2	15.3	10.7	19.6	29.6
		2	18.8	7.87	19.2	12.97	14.2	17.5	17.4	17.9		
		3	28.8	5.14	29.4	7.45	20.2	13.7	26.1	18.4		
	5	1	2.8	46.4	3.4	53.5	6.0	26.3	4.1	50.0	7.8	79.5
		2	15.6	17.3	17.6	9.5	14.8	13.9	16.0	14.8		
		3	3.4	33.5	3.0	23.7	3.6	50.6	3.3	37.3		
E. faecalis	3	1	326.0	9.0	317.6	3.6	292.8	1.8	312.1	7.2	271.1	18.6
		2	208.0	3.0	201.6	3.3	203.2	1.8	204.3	2.9		
		3	310.2	1.8	285.0	2.6	295.4	1.7	296.9	4.1		
	4	1	33.6	11.0	33.2	6.5	24.2	15.3	30.3	17.9	36.7	19.3
		2	45.0	10.1	41.8	13.0	41.2	4.7	42.7	10.0		
		3	41.6	11.9	35.6	14.9	33.8	5.7	37.0	14.3		
	5	1	8.4	18.1	7.0	20.1	4.4	34.5	6.6	33.3	9.6	38.5
		2	8.4	27.4	9.4	17.8	8.8	14.8	8.9	19.4		
		3	14.4	18.8	14.6	20.9	11.4	17.1	13.5	21.1		
Saline	NA	1	0.0	NA	0.2	225	0.0	NA	0.1	260.0	0.0	NA
		2	0.0	NA	0.0	NA	0.0	NA	0.0	NA		
		3	0.0	NA	0.0	NA	0.2	225.0	0.1	260.0		

NA: Not Applicable; %CV: Percent Coefficient of Variation

[1] $\log_{10}$-fold dilution of 0.5 McFarland standard suspension

Table 6. Reproducibility of colony counts on MacConkey agar obtained by the APAS Compact with Urine Analysis Module

Species	Dilution [1]	Replicate	Instrument 1		Instrument 2		Instrument 3		Overall			
			Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV
E. coli	3	1	152.2	3.0	140.2	3.2	140.2	2.3	144.2	4.8	182.4	22.5
		2	174.6	4.5	162.4	1.3	160.0	1.8	165.7	4.9		
		3	247.2	2.1	233.0	3.4	231.8	2.8	237.3	4.0		
	4	1	48.2	5.4	41.0	1.7	42.4	5.9	43.9	8.6	45.5	7.5
		2	48.8	3.9	49.2	2.2	47.6	3.2	48.5	3.3		
		3	44.2	2.5	44.6	7.9	43.6	3.5	44.1	4.9		
	5	1	4.2	20.0	4.6	19.3	3.8	28.9	4.2	22.4	4.6	65.2
		2	2.0	0.0	1.0	0.0	1.0	0.0	1.3	37.7		
		3	8.8	21.8	7.6	20.0	8.2	15.9	8.2	19.1		
Saline	1	1	0.0	NA	0.0	NA	0.0	NA	0.0	NA	0.1	400.0
		2	0.0	NA	0.0	NA	0.0	NA	0.0	NA		
		3	1.0	71.0	0.2	225.0	0.0	NA	0.4	157.5		

NA: Not Applicable; %CV: Percent Coefficient of Variation
[1] $\log_{10}$-fold dilution of 0.5 McFarland standard suspension

b. Linearity/assay reportable range:

To determine the accuracy of colony counts obtained using the APAS Compact with Urine Analysis Module, a study was conducted using 10-fold serial dilutions of bacterial cultures that were plated on blood and/or MacConkey agar, as appropriate to the organism/organism combination. The plates were incubated and read independently by two microbiologists who each estimated colony counts. The mean of the two manual counts was used as the reference result for each plate. Each plate was also analyzed in 5 different orientations using APAS Compact with Urine Analysis Module (0, 60, 120, 180 and 270°). Note: plates that exhibited no growth on initial reading were imaged once and were not rotated to different orientations. The individual APAS Compact colony counts obtained with each plate in each orientation were compared to those obtained by the manual reference method. For analysis of the data, counts obtained by both APAS Compact and the reference method were each grouped into four categories as shown below:

Colonies/plate	Category (CFU/mL) [1]
0	No Growth
1-9	10^3
10-99	10^4
≥100	$\geq 10^5$

[1] Based on a 1µL inoculum volume

The results presented in **Tables 7** and **8** show that all low counts obtained by APAS Compact with Urine Analysis Module were within 1-$\log_{10}$ of those obtained by the manual reference method. APAS Compact did not incorrectly designate any of the cultures with growth as "Negative" and there were several cases in which APAS Compact designated plates as positive for growth (i.e., $\geq 10^3$ CFU/mL) but for which no growth was reported by the reference method. Together with the results of the Clinical Study in **Section L(3)**, these data indicate that there is low probability that the APAS Compact with Urine Analysis Module will produce false negative results due to the failure to detect visible microbial colonies. In addition, because any growth detected by the APAS Compact is subject to follow-up by a trained microbiologist, the risk to patients from incorrect assignment of colony counts by the instrument is mitigated. The results of this study are therefore acceptable and provide evidence of the accuracy of colony counts obtained using the APAS Compact with Urine Analysis Module.

Table 7. Correlation of colony count categories obtained on blood agar using the APAS Compact with Urine Analysis Module and the manual reference method

E. coli		**Reference Method (CFU/mL)**				
		No Growth	**10^3**	**10^4**	**$\geq 10^5$**	**Total**
APAS (CFU/mL)	**No Growth**	**0**	0	0	0	**0**
	10^3	3	**37**	2	0	**42**
	10^4	0	8	**50**	5	**63**
	$\geq 10^5$	0	0	13	**110**	**123**
	Total	**3**	**45**	**65**	**115**	**228**
% APAS < Manual		NA	0	3.1	4.3	
% APAS = Manual		0	82.2	76.9	95.7	
% APAS > Manual		100	17.8	20.0	NA	

E. faecalis		**Reference Method (CFU/mL)**				
		No Growth	**10^3**	**10^4**	**$\geq 10^5$**	**Total**
APAS (CFU/mL)	**No Growth**	0	0	0	0	**0**
	10^3	14	43	0	0	**57**
	10^4	0	37	10	0	**47**
	$\geq 10^5$	0	0	45	105	**150**
	Total	**14**	**80**	**55**	**105**	**254**
% APAS < Manual		NA	0	0	0	
% APAS = Manual		0	53.8	18.2	100	
% APAS > Manual		100	46.3	81.8	NA	

P. vulgaris		**Reference Method (CFU/mL)**				
		No Growth	**10^3**	**10^4**	**$\geq 10^5$**	**Total**
APAS (CFU/mL)	**No Growth**	0	0	0	0	**0**
	10^3	8	54	2	0	**64**
	10^4	3	1	73	30	**107**
	$\geq 10^5$	0	0	0	80	**80**
	Total	**11**	**55**	**75**	**110**	**251**
% APAS < Manual		NA	0	2.7	27.3	
% APAS = Manual		0	98.2	97.3	72.7	
% APAS > Manual		100	1.8	0.0	NA	

P. aeruginosa		**Reference Method (CFU/mL)**				
		No Growth	**10^3**	**10^4**	**$\geq 10^5$**	**Total**
APAS (CFU/mL)	**No Growth**	**0**	0	0	0	**0**
	10^3	0	**38**	0	0	**38**
	10^4	0	21	**32**	0	**53**
	$\geq 10^5$	0	0	23	**125**	**148**
	Total	**0**	**59**	**55**	**125**	**239**
% APAS < Manual		NA	0	0	0	
% APAS = Manual		NA	64.4	58.2	100	
% APAS > Manual		NA	35.6	41.8	NA	

S. saprophyticus		Reference Method (CFU/mL)				
		No Growth	**10^3**	**10^4**	**$\geq 10^5$**	**Total**
APAS (CFU/mL)	**No Growth**	**0**	0	0	0	**0**
	10^3	10	**79**	0	0	**89**
	10^4	5	1	**50**	5	**61**
	$\geq 10^5$	0	0	0	**95**	**95**
	Total	**15**	**80**	**50**	**100**	**245**
% APAS < Manual		NA	0	0	5.0	
% APAS = Manual		0	98.8	100	95.0	
% APAS > Manual		100	1.3	0	NA	

E. coli/E. faecalis [1]		Reference Method (CFU/mL)				
		No Growth	**10^3**	**10^4**	**$\geq 10^5$**	**Total**
APAS (CFU/mL)	**No Growth**	**0**	0	0	0	**0**
	10^3	9	**47**	5	0	**61**
	10^4	0	21	**65**	8	**94**
	$\geq 10^5$	0	0	0	**92**	**92**
	Total	**9**	**68**	**70**	**100**	**245**
% APAS < Manual		NA	0	7.1	8.0	
% APAS = Manual		0	69.1	92.9	92.0	
% APAS > Manual		100	30.9	0	NA	

E. coli/P. vulgaris/ G. vaginalis [2]		Reference Method (CFU/mL)				
		No Growth	**10^3**	**10^4**	**$\geq 10^5$**	**Total**
APAS (CFU/mL)	**No Growth**	**0**	0	0	0	**0**
	10^3	5	**61**	0	0	**66**
	10^4	0	14	**55**	15	**84**
	$\geq 10^5$	0	0	0	**85**	**85**
	Total	**5**	**75**	**55**	**100**	**235**
% APAS < Manual		NA	0	0	15.0	
% APAS = Manual		0	81.3	100	85.0	
% APAS > Manual		100	18.7	0	NA	

NA: Not Applicable

[1] Manual inspection of culture plates determined the presence of colonies of both *E. coli* and *E. faecalis* in a ratio of approximately 2:1

[2] Manual inspection of culture plates determined the presence of colonies of both *E. coli* and *P. vulgaris* in approximately equal numbers (1:1 ratio). However, no colonies with morphology consistent with *G. vaginalis* were observed.

Table 8. Correlation of colony count categories obtained on MacConkey agar using the APAS Compact with Urine Analysis Module and the manual reference method

E. coli		Reference Method (CFU/mL)				
		No Growth	**10^3**	**10^4**	**$\geq 10^5$**	**Total**
APAS (CFU/mL)	**No Growth**	0	0	0	0	**0**
	10^3	0	56	0	0	**56**
	10^4	0	19	65	0	**84**
	$\geq 10^5$	0	0	5	105	**110**
	Total	**0**	**75**	**70**	**105**	**250**
% APAS < Manual		NA	0	0	0	
% APAS = Manual		NA	74.7	92.9	100	
% APAS > Manual		NA	25.3	7.1	NA	

P. aeruginosa		Reference Method (CFU/mL)				
		No Growth	**10^3**	**10^4**	**$\geq 10^5$**	**Total**
APAS (CFU/mL)	**No Growth**	**0**	0	0	0	**0**
	10^3	0	**29**	0	0	**29**
	10^4	0	26	**40**	5	**71**
	$\geq 10^5$	0	0	35	**69**	**104**
	Total	**0**	**55**	**75**	**74**	**204**
% APAS < Manual		NA	0	0	6.8	
% APAS = Manual		NA	52.7	53.3	93.2	
% APAS > Manual		NA	47.3	46.7	NA	

P. vulgaris		Reference Method (CFU/mL)				
		No Growth	**10^3**	**10^4**	**$\geq 10^5$**	**Total**
APAS (CFU/mL)	**No Growth**	**0**	0	0	0	**0**
	10^3	0	**64**	9	0	**73**
	10^4	0	1	**61**	7	**69**
	$\geq 10^5$	0	0	0	**103**	**103**
	Total	**0**	**65**	**70**	**110**	**245**
% APAS < Manual		NA	0	12.9	6.4	
% APAS = Manual		NA	98.5	87.1	93.6	
% APAS > Manual		NA	1.5	0	NA	

NA: Not Applicable

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

The instructions for use indicate that the APAS Compact requires daily calibration using a dedicated optical tool that is provided with the instrument. Daily calibration of the instruments was performed throughout the analytical and clinical studies that were conducted to evaluate the performance of the device. None of the instruments failed calibration during the course of these studies.

In addition to daily optical calibration, the instructions for use indicate that operators should also perform a daily functional quality control check with cultures of *Enterococcus faecalis* and *Escherichia coli* grown on blood and MacConkey agar, respectively. In order to pass, the results from both culture media must meet the prescribed acceptance criteria for colony count and morphological designation. In

addition, uninoculated plates of both types should exhibit no growth. **Table 9** shows the results obtained from Quality Controls runs performed during the APAS Compact clinical studies. The expected results were obtained with all (100%) positive controls on both blood and MacConkey agar. For the negative controls, the expected results were obtained with 98.4% on blood agar and 100% on MacConkey agar.

Table 9. Results of Quality Control testing performed during the APAS Compact clinical studies

Site	Instrument	Positive Control			Negative Control		
		Tested	Expected Result (%)		Tested	Expected Result (%)	
			Blood	MacConkey		Blood	MacConkey
1	1 [1]	50	50 (100)	50 (100)	50	49 (98.0) [3]	50 (100)
	2 [2]	49	49 (100)	49 (100)	49	49 (100)	49 (100)
2	3	13	13 (100)	13 (100)	Note Done [4]	Not Done	Not Done
3	4	29	29 (100)	29 (100)	30	29 (96.7) [3]	30 (100)
	Total	**141**	**141 (100)**	**141 (100)**	**129**	**127 (98.4)**	**129 (100)**

[1] 1 Negative Control for blood agar and 1 for MacConkey agar gave positive results due to artifacts on the plate. Positive and Negative QC runs for both days were repeated successfully.

[2] 2 Negative Controls for blood agar gave positive results due to artifacts on the plate. Positive and Negative QC runs for that day were repeated successfully.

[3] Both Negative Control failures on blood agar were due to the presence of a single contaminating colony.

[4] The study at Site 2 was completed prior to the implementation of daily Negative Control testing.

d. Detection Limit:

Detection of colonies by the APAS Compact is, in part, dependent upon colony size. A study was therefore conducted using a representative panel of UTI pathogens to determine the effect of colony size of the ability to detect growth. The organisms in the study were selected to include species that exhibit each of the characteristic morphologies used by the Urine Analysis Module software for designation of results.

Each organism in the study was diluted to different concentrations and inoculated onto blood and/or MacConkey agar plates which were incubated at 35±2°C until pin point colonies were visible to the naked eye. Images of the plates were then captured by the APAS Compact and the operator digitally labeled multiple isolated colonies to measure their diameter. The image of each plate was then analyzed using the Urine Analysis Module software to generate the corresponding APAS Compact result. The measurements of the colonies that were successfully detected by the APAS Compact were used to calculate the minimum colony size for each organism that could be detected with 95% probability. Results of the study are presented in **Tables 10** and **11** and demonstrate the limits of colony size that can be detected reliably by the APAS Compact with Urine Analysis Module.

Table 10. Limits of detection (LOD) of the APAS Compact with Urine Analysis Module for organisms cultured on blood agar

	Detected			Not Detected			LOD in mm (95% CI)
	N	Colony Diameter (mm)		N	Colony Diameter (mm)		
		Min	Max		Min	Max	
Aerococcus viridans	141	0.272	1.268	81	0.272	1.178	1.258 (1.049, 1.692)
Enterococcus faecalis	225	0.181	1.178	165	0.181	1.087	0.856 (0.776, 0.980)
Escherichia coli	240	0.181	1.721	123	0.181	0.906	0.899 (0.821, 1.024)
Proteus mirabilis	140	0.634	2.808	281	0.181	2.717	2.501 (2.168, 3.091)
Pseudomonas aeruginosa	238	0.453	3.442	153	0.181	2.355	4.037 (2.881, 7.121)
Staphylococcus saprophyticus	121	0.362	0.996	98	0.181	0.906	0.877 (0.784, 1.049)
Streptococcus agalactiae	120	0.362	0.725	138	0.181	0.725	0.625 (0.584, 0.697)

N: number of colonies; Min: minimum; Max: maximum

Table 11. Limits of detection (LOD) of the APAS Compact with Urine Analysis Module for organisms cultured on MacConkey agar

	Detected			Not Detected			LOD in mm (95% CI)
	N	Colony Diameter (mm)		N	Colony Diameter (mm)		
		Min	Max		Min	Max	
Escherichia coli	112	0.996	2.264	136	0.362	1.178	1.253 (1.214, 1.324)
Morganellla morganii	170	0.634	1.721	170	0.272	1.268	1.262 (1.164, 1.421)
Pseudomonas aeruginosa	48	0.634	2.989	78	0.181	1.087	1.170 (1.020, 1.596)
Serratia marcescens	76	0.725	1.087	296	0.181	1.087	1.613 (1.398, 2.093)

N: number of colonies; Min: minimum; Max: maximum

e. Analytical Specificity:

The ability of the APAS Compact with Urine Analysis Module to assign the appropriate colony morphology to different clinically relevant organisms associated with UTIs was evaluated by testing serial dilutions of both pure and mixed cultures. Dilutions of each organism or organism combination were inoculated in triplicate onto the appropriate culture plates which were incubated at 35±2°C for 18 hours. The APAS Compact was used to capture images of plates that exhibited 1-100 individual colonies or areas of confluent growth and >100 isolated colonies. Each plate was read on the APAS Compact instrument in 3 different orientations (0, 120 and 270°). The plates were then re-incubated and imaged again after 20 and 22 hours. Results for assignment of colony morphology are shown for pure and mixed cultures below in **Tables 12-15**. The percentage of plate images with at least one colony of the expected morphology is reported as agreement.

Pure Cultures

With pure cultures on blood agar, the APAS Compact with Urine Analysis Module reported detection of the expected colony morphology on each image for all the species tested at each time point except with *Aerococcus urinae*, *Lactobacillus rhamnosus*, *Pseudomonas aeruginosa* and *Staphylococcus epidermidis* (**Table 12**). For all species except *A. urinae* and *L. rhamnosus*, the APAS Compact designation of each plate at each time point was either "Positive" or "Review."

For *S. marcescens* on MacConkey agar, the expected morphology was observed on all plates after 20 and 22 hours of incubation but not after 18 hours (**Table 13**). All images of cultures on MacConkey agar were designated as "Positive" by the APAS Compact.

Table 12. Detection of expected colony morphology by the APAS Compact with Urine Analysis Module: pure cultures on blood agar

Species	Expected Colony Morphology	Agreement [1]	
		Number/Total	Percent
Aerococcus urinae	Small, alpha hemolytic	53/54	98.1 [2]
Aerococcus viridans	Small, alpha hemolytic	54/54	100
Candida albicans	Small	54/54	100
Enterobacter cloacae	Coliform	54/54	100
Escherichia coli (strain 1)	Coliform	54/54	100
Escherichia coli (strain 2)	Coliform	54/54	100
Enterococcus faecalis	Small	54/54	100
Klebsiella pneumoniae	Coliform	52/52	100
Lactobacillus rhamnosus	Small	6/27	22.2 [3]
Morganella morganii	Coliform	54/54	100
Proteus mirabilis	Swarming	54/54	100
Pseudomonas aeruginosa	Granular	50/51	98.0 [4]
Staphylococcus aureus	Cream white	54/54	100
Staphylococcus epidermidis	Cream white	38/54	70.4 [5]
Staphylococcus saprophyticus	Cream white	51/51	100
Streptococcus agalactiae	Beta-hemolytic	54/54	100
Streptococcus dysgalactiae	Beta-hemolytic	51/51	100

Note: The APAS Compact designation of each plate at each time point was either "Positive" or "Review" for all species except *A. urinae* and *L. rhamnosus*

[1] Number of plate images with at least one colony of the expected morphology (all time points and plate rotations combined)/total

[2] Expected morphology detected: 18 hours: 18/18 (88.9%); 20 hours: 18/18 (100%); 22 hours: 17/18 (94.4%)

[3] Expected morphology detected: 18 hours: 0/9 (0%); 20 hours: 0/9 (0%); 22 hours: 6/9 (66.7%)

[4] Expected morphology detected: 18 hours: 18/18 (100%); 20 hours: 17/18 (94.4%); 22 hours: 15/15 (100%)

[5] Expected morphology detected: 18 hours: 9/18 (50.0%); 20 hours: 11/18 (61.1%); 22 hours: 18/18 (100%)

Table 13. Detection of expected colony morphology by the APAS Compact with Urine Analysis Module: pure cultures on MacConkey agar

Species	Expected Colony Morphology	Agreement [1]	
		Number/Total	Percent
Citrobacter koseri	Non-fermenter	53/53	100
Escherichia coli	Lactose fermenter	54/54	100
Klebsiella pneumoniae	Lactose fermenter	54/54	100
Morganella morganii	Non-fermenter	54/54	100
Serratia marcescens [2]	Red pigment	21/27	77.8

Note: All plate images of pure cultures on MacConkey agar were designated by APAS Compact as "Positive"
[1] Number of plate images with at least one colony of the expected morphology (all time points and plate rotations combined)/total
[2] Expected morphology detected: 3/9 (33.3%); 20 hours: 9/9 (100%); 22 hours: 9/9 (100%)

Mixed Cultures

For blood agar plates inoculated with two organisms at a 1:1 ratio, the APAS Compact reported detection of both the expected colony types at each time point in all but two images (**Table 14**). In both cases, the APAS Compact failed to detect the expected morphology for *S. agalactiae* in the presence of *E. faecalis*, although both images were reported as "Positive" indicating of the need for microbiological follow-up. With plates inoculated using a 1:10 ratio of *S. agalactiae*:*E. faecalis* there was a higher proportion of images in which colonies with the characteristic morphology of *S. agalactiae* were not detected. Nevertheless, all the images were still reported as "Positive."

For mixed cultures plated on MacConkey agar, both the expected colony types were detected in all but 1 image, although this image was still reported "Positive" by the instrument (**Table 15**).

Note: Because any growth detected by the APAS Compact with Urine Analysis Module is subject to follow-up by a trained microbiologist, the risk to patients from incorrect assignment of colony morphology by the instrument is mitigated.

Instructions for appropriate laboratory follow-up of any growth detected by the APAS Compact with Urine Analysis Module are included in the device labeling.

Table 14. Detection of expected colony morphology by the APAS Compact with Urine Analysis Module: mixed cultures on blood agar

Species Name & Expected Morphology				Mixture [1]	Agreement (%) [2]	
Species 1		Species 2			Species 1	Species 2
Escherichia coli	Coliform	*Enterococcus faecalis*	Small	1:1	63/63 (100)	63/63 (100)
				1:10	81/81 (100)	81/81 (100)
Streptococcus agalactiae	Beta-hemolytic	*Enterococcus faecalis*	Small	1:1	81/81 (100)	81/81 (100)
				1:10	28/63 (44.4) [3]	63/63 (100)
Escherichia coli	Coliform	*Staphylococcus saprophyticus*	Cream white	1:1	54/54 (100)	54/54 (100)
				1:10	81/81 (100)	81/81 (100)
Escherichia coli	Coliform	*Aerococcus viridans*	Alpha-hemolytic	1:1	81/81 (100)	81/81 (100)
				1:10	81/81 (100)	81/81 (100)

Note: All plate images of mixed cultures on blood agar were designated by APAS Compact as "Positive"
[1] Approximate ratio of concentration, Species 1:Species 2
[2] Number of plate images with at least one colony of the expected morphology (all time points and plate rotations combined)/total
[3] Expected morphology detected: 18 hours: 12/21 (57.1%); 20 hours: 10/21 (47.6%); 22 hours: 6/21 (28.6%)

Table 15. Detection of expected colony morphology by the APAS Compact with Urine Analysis Module: mixed cultures on MacConkey agar

Species Name & Expected Morphology				Mixture [1]	Agreement (%) [2]	
Species 1		Species 2			Species 1	Species 2
Escherichia coli	Lactose Fermenter	*Morganella morganii*	Non-fermenter	1:1	53/53 (100)	53/53 (100)
				1:10	79/80 (98.8) [3]	80/80 (100)
Escherichia coli	Lactose Fermenter	*Pseudomonas aeruginosa*	Non-fermenter	1:1	81/81 (100)	81/81 (100)
				1:10	72/72 (100)	72/72 (100)

Instances of agreement with the expected morphology <100% are shaded
Note: All images of mixed cultures on MacConkey agar were designated by APAS Compact as "Positive"
[1] Approximate ratio of concentration, Species 1:Species 2
[2] Number of plate images with at least one colony of the expected morphology (all time points and plate rotations combined)/total
[3] Expected morphology detected: 18 hours: 25/26 (96.2%); 20 hours: 27/27 (100%); 22 hours: 27/27 (100%)

f. Assay Cut-off:

Not applicable.

2. Comparison studies:

a. Method comparison with predicate device:

Not applicable. Refer to **Section L(3), Clinical Studies**.

b. Matrix comparison:

Not applicable.

3. Clinical Studies:

a. Clinical Sensitivity:

To evaluate the performance of the APAS Compact with Urine Analysis Module, clinical studies were conducted at three sites (1 US and 2 ex-US) using remnant urine samples that were leftover from standard of care culture for suspected UTI. Each urine sample was inoculated onto one sheep blood agar and one MacConkey agar culture plate (both Remel) that were incubated for 18 hours at 35±2°C prior to analysis by the APAS Compact and by an independent panel of three microbiologists. Results were reported by the Urine Analysis Module software as "Negative," "Review" or "Positive" as described in **Table 4**, above. For the analysis of performance, APAS Compact designations of "Review" and "Positive" were regarded as positive. For the reference method, each microbiologist was trained to read the urine culture plates in a standard fashion and was blinded to the results from the other panel members and to those obtained by the APAS Compact.

Only urine samples from "uncomplicated" cases of suspected UTI were included in the analysis of performance (i.e., those not obtained from subjects with known underlying urinary tract pathology, suspected cases of persistent urinary tract infection, urine collected by invasive procedures or urine samples from immunocompromised subjects). A summary of the reasons for exclusion of samples from the performance calculations is shown in **Table 16**.

Table 16. Number of urine samples enrolled at each clinical site and reasons for exclusion from the analysis of performance

Description	**Site** [1]			**Total**
	1	**2**	**3**	
Enrolled	5835	2117	2148	**10100**
Included	5634	1769	1821	**9224**
Excluded	201	348	327	**876**
Reasons for exclusion				
Complicated UTI	29	0	0	**29**
Read time [1]	156	0	235	**391**
Incomplete record	16	6	92	**114**
LIMS Flag [2]	0	342	0	**342**

[1] Site 1: US; Sites 2 and 3: ex-US
[2] Culture plates not read within specified timeframe after incubation
[2] Additional data from Laboratory Information Management System (LIMS) used in algorithm for sample disposition (e.g., white cell count)

Tables 17 and **18** summarize the demographic characteristics of the subjects enrolled at each clinical site. The majority of urine samples were from female donors, which is consistent with the higher prevalence of UTIs in the female population. Samples were

enrolled from subjects ranging from ≤20 to ≥80 years of age, with the majority from subjects between 20 and 79 years of age.

Table 17. Gender distribution of donors of urine samples enrolled in the clinical studies

Site [1]	Male	Female	Not Known	Total	% Male	% Female
1	972	4659	3	**5634**	17.3	82.7
2	702	1066	1	**1769**	39.7	60.3
3	810	1007	4	**1821**	44.6	55.4
Total	**2484**	**6732**	**8**	**9224**	**27.0**	**73.0**

[1] Site 1: US; Sites 2 and 3: ex-US

Table 18. Age distribution of urine sample donors in the clinical studies

Age (years)	Site [1]			Total	%
	1	2	3		
≤20	747	154	97	**998**	**10.8**
20-39	1611	415	458	**2384**	**25.9**
40-59	1247	440	450	**2137**	**23.2**
60-79	1460	548	614	**2622**	**28.4**
≥80	567	212	300	**1079**	**11.7**
Not Known	2	0	2	**4**	**0.0**
	5634	**1769**	**1821**	**9224**	**100**

[1] Site 1: US; Sites 2 and 3: ex-US

A summary of the APAS Compact designation for samples from the clinical studies in relation to colony counts as determined by the reference microbiologist panel is shown in **Tables 19-21**. Colony counts by both methods were categorized as described in **Section L(1)(b)**. Across all sites combined, the APAS Compact correctly designated 99.0% (95% confidence interval: 98.7-99.2%) of cultures on blood agar and 99.5% (95% CI: 99.2-99.7%) of cultures on MacConkey agar as positive for growth. Depending on the colony count observed by the microbiologist panel, the false negative rate for detection of microbial growth on blood agar ranged from 0% to 2.9% and on MacConkey agar from 0% to 1.3%.

False-negative results with the APAS Compact for the detection of growth could lead to discard of culture plates without further review. The results of this study demonstrate that the likelihood of such results is acceptably low.

Tables 22, 23 and **24** show the correlation of colony count categories obtained by the APAS Compact and by the reference method. In general, the colony count categories reported by the APAS Compact were the same or higher than those obtained by the reference method, and there were multiple instances in which APAS Compact designated plates that exhibited "No Growth" according to the reference method as "Positive" or "Review." This is acceptable because all cultures designated by APAS Compact as "Positive" or "Review" are subject to further microbiological follow-up and any such incorrect designations do not increase risks to patients.

Table 19. Performance of the APAS Compact with Urine Analysis Module for detection of growth on blood agar

Site [1]	Reference Result	APAS Designation			Total	Correct [2]	% Correct (95% CI)
		Negative	Review	Positive			
1	No Growth	1220	14	256	1490	1220	81.9 (79.8, 83.8)
	10^3 CFU/mL	37	393	845	1275	1238	97.1 (96.0, 97.9)
	10^4 CFU/mL	4	1089	74	1167	1163	99.7 (99.1, 99.9)
	$\geq 10^5$ CFU/mL	0	1700	2	1702	1702	100 (99.8, 100)
	Any Growth	41	3182	921	4144	4103	99.0 (98.7, 99.3)
2	No Growth	438	18	57	513	438	85.4 (82.1, 88.2)
	10^3 CFU/mL	13	152	308	473	460	97.3 (95.4, 98.4)
	10^4 CFU/mL	2	461	25	488	486	99.6 (98.5, 99.9)
	$\geq 10^5$ CFU/mL	0	295	0	295	295	100 (98.7, 100)
	Any Growth	15	908	333	1256	1241	98.8 (98.0, 99.3)
3	No Growth	574	2	61	637	574	90.1 (87.5, 92.2)
	10^3 CFU/mL	8	101	262	371	363	97.8 (95.8, 98.9)
	10^4 CFU/mL	2	355	23	380	378	99.5 (98.1, 99.9)
	$\geq 10^5$ CFU/mL	3	422	8	433	430	99.3 (98.0, 99.8)
	Any Growth	13	878	293	1184	1171	98.9 (98.1, 99.4)
Total	No Growth	2232	34	374	2640	2232	84.5 (83.1, 85.9)
	10^3 CFU/mL	46	646	1415	2119	2061	97.3 (96.5, 97.9)
	10^4 CFU/mL	8	1905	122	2035	2027	99.6 (99.2, 99.8)
	$\geq 10^5$ CFU/mL	3	2417	10	2430	2427	99.9 (99.6, 100)
	Any Growth	69	4968	1547	6584	6515	99.0 (98.7, 99.2)

CI: 95% score Confidence Interval

[1] Site 1: US; Sites 2 and 3: ex-US

[2] For the purposes of data analysis, APAS Compact designations of "Review" and "Positive" were both considered indicative of microbial growth.
For a Reference Result of No Growth, an APAS Compact designation of "Negative" was considered correct.
For Reference Results of 10^3, 10^4, $\geq 10^5$ CFU/mL or Any Growth, an APAS Compact designation of "Positive" or "Review" was considered correct.

Table 20. Performance of the APAS Compact with Urine Analysis Module for detection of growth on MacConkey agar

Site [1]	Reference Result	APAS Designation			Total	Correct	% Correct [2] (95% CI)
		Negative	Review	Positive			
1	No Growth	3274	23	37	3334	3274	98.2 (97.7, 98.6)
	10^3 CFU/mL	6	406	67	479	473	98.7 (97.3, 99.4)
	10^4 CFU/mL	1	469	8	478	477	99.8 (98.8, 100)
	$\geq 10^5$ CFU/mL	2	1341	0	1343	1341	99.9 (99.5, 100)
	Any Growth	9	2216	75	2300	2291	99.6 (99.3, 99.8)
2	No Growth	1257	4	4	1265	1257	99.4 (98.8, 99.7)
	10^3 CFU/mL	2	136	48	186	184	98.9 (96.2, 99.7)
	10^4 CFU/mL	1	152	1	154	153	99.4 (96.4, 99.9)
	$\geq 10^5$ CFU/mL	0	164	0	164	164	100 (97.7, 100)
	Any Growth	3	452	49	504	501	99.4 (98.3, 99.8)
3	No Growth	1241	2	0	1243	1241	99.8 (99.4, 100)
	10^3 CFU/mL	3	105	39	147	144	98.0 (94.2, 99.3)
	10^4 CFU/mL	1	144	1	146	145	99.3 (96.2, 99.9)
	$\geq 10^5$ CFU/mL	0	285	0	285	285	100 (98.7, 100)
	Any Growth	4	534	40	578	574	99.3 (98.2, 99.7)
Total	No Growth	5772	29	41	5842	5772	98.8 (98.5, 99.1)
	10^3 CFU/mL	11	647	154	812	801	98.6 (97.6, 99.2)
	10^4 CFU/mL	3	765	10	778	775	99.6 (98.9, 99.9)
	$\geq 10^5$ CFU/mL	2	1790	0	1792	1790	99.9 (99.6, 100)
	Any Growth	16	3202	164	3382	3366	99.5 (99.2, 99.7)

CI: 95% score Confidence Interval

[1] Site 1: US; Sites 2 and 3: ex-US

[2] For the purposes of data analysis, APAS Compact designations of "Review" and "Positive" were both considered indicative of microbial growth.
For a Reference Result of No Growth, an APAS Compact designation of "Negative" was considered correct.
For Reference Results of 10^3, 10^4, $\geq 10^5$ CFU/mL or Any Growth, an APAS Compact designation of "Positive" or "Review" was considered correct.

Table 21. Performance of the APAS Compact with Urine Analysis Module for detection of growth by sample (blood and MacConkey agars combined)

Site [1]	Reference Result	APAS Designation			Total	Correct	% Correct [2] (95% CI)
		Negative	Review	Positive			
1	No Growth	1166	25	261	1452	1166	80.3 (78.2, 82.3)
	10^3 CFU/mL	37	463	780	1280	1243	97.1 (96.0, 97.9)
	10^4 CFU/mL	4	1104	64	1172	1168	99.7 (99.1, 99.9)
	$\geq 10^5$ CFU/mL	0	1729	1	1730	1730	100 (99.8, 100)
	Any Growth	41	3296	845	4182	4141	99.0 (98.7, 99.3)
2	No Growth	429	19	57	505	429	85.0 (81.6, 87.8)
	10^3 CFU/mL	13	166	300	479	466	97.3 (95.4, 98.4)
	10^4 CFU/mL	1	464	25	490	489	99.8 (98.9, 100)
	$\geq 10^5$ CFU/mL	0	295	0	295	295	100 (98.7, 100)
	Any Growth	14	925	325	1264	1250	98.9 (98.1, 99.3)
3	No Growth	555	3	60	618	555	89.8 (87.2, 92.0)
	10^3 CFU/mL	9	115	262	386	377	97.7 (95.6, 98.8)
	10^4 CFU/mL	2	356	23	381	379	99.5 (98.1, 99.9)
	$\geq 10^5$ CFU/mL	3	426	7	436	433	99.0 (98.0, 99.8)
	Any Growth	14	897	292	1203	1189	98.8 (98.1, 99.3)
Total	No Growth	2150	47	378	2575	2150	83.5 (96.7, 99.1)
	10^3 CFU/mL	59	744	1342	2145	2086	97.2 (96.5, 97.9)
	10^4 CFU/mL	7	1924	112	2043	2036	99.7 (99.3, 99.8)
	$\geq 10^5$ CFU/mL	3	2450	8	2461	2458	99.9 (99.6, 100)
	Any Growth	69	5118	1462	6649	6580	99.0 (98.7, 99.2)

CI: 95% score Confidence Interval

[1] Site 1: US; Sites 2 and 3: ex-US

[2] For the purposes of data analysis, APAS Compact designations of "Review" and "Positive" were both considered indicative of microbial growth.
For a Reference Result of No Growth, an APAS Compact designation of "Negative" was considered correct.
For Reference Results of 10^3, 10^4, $\geq 10^5$ CFU/mL or Any Growth, an APAS Compact designation of "Positive" or "Review" was considered correct.

Table 22. Correlation of colony count categories obtained on blood agar by the APAS Compact with Urine Analysis Module and the manual reference method

Site 1 (US)		**Reference Method (CFU/mL)**				
		No Growth	**10^3**	**10^4**	**$\geq 10^5$**	**Total**
APAS (CFU/mL)	**No Growth**	1220	37	4	0	**1261**
	10^3	262	1049	87	2	**1400**
	10^4	7	182	828	27	**1044**
	$\geq 10^5$	1	7	248	1673	**1929**
	Total	**1490**	**1275**	**1167**	**1702**	**5634**
% APAS < Reference		NA	2.9	7.8	1.7	
% APAS = Reference		81.9	82.3	71.0	98.3	
% APAS > Reference		18.1	14.8	21.3	NA	
Site 2 (ex-US)		**Reference Method (CFU/mL)**				
		No Growth	**10^3**	**10^4**	**$\geq 10^5$**	**Total**
APAS (CFU/mL)	**No Growth**	438	13	2	0	**453**
	10^3	68	388	31	1	**488**
	10^4	7	63	368	21	**459**
	$\geq 10^5$	0	9	87	273	**369**
	Total	**513**	**473**	**488**	**295**	**1769**
% APAS < Reference		NA	2.7	6.8	7.5	
% APAS = Reference		85.4	82.0	75.4	92.5	
% APAS > Reference		14.6	15.2	17.8	NA	
Site 3 (ex-US)		**Reference Method (CFU/mL)**				
		No Growth	**10^3**	**10^4**	**$\geq 10^5$**	**Total**
APAS (CFU/mL)	**No Growth**	574	8	2	3	**587**
	10^3	63	312	27	8	**410**
	10^4	0	45	245	12	**302**
	$\geq 10^5$	0	6	106	410	**522**
	Total	**637**	**371**	**380**	**433**	**1821**
% APAS < Reference		NA	2.2	7.6	5.3	
% APAS = Reference		90.1	84.1	64.5	94.7	
% APAS > Reference		9.9	13.7	27.9	NA	
All Sites Combined		**Reference Method (CFU/mL)**				
		No Growth	**10^3**	**10^4**	**$\geq 10^5$**	**Total**
APAS (CFU/mL)	**No Growth**	2232	58	8	3	**2301**
	10^3	393	1749	145	11	**2298**
	10^4	14	290	1441	60	**1805**
	$\geq 10^5$	1	22	441	2356	**2820**
	Total	**2640**	**2119**	**2035**	**2430**	**9224**
% APAS < Reference		NA	2.7	7.5	3.0	
% APAS = Reference		84.5	82.5	70.8	97.0	
% APAS > Reference		15.5	14.7	21.7	NA	

NA: Not Applicable

Table 23. Correlation of colony count categories obtained on MacConkey agar by the APAS Compact with Urine Analysis Module and the manual reference method

Site 1 (US)		Reference Method (CFU/mL)				
		No Growth	**10^3**	**10^4**	**$\geq 10^5$**	**Total**
APAS (CFU/mL)	**No Growth**	3274	6	1	2	**3283**
	10^3	56	440	11	0	**507**
	10^4	4	33	407	38	**482**
	$\geq 10^5$	0	0	59	1303	**1362**
	Total	**3334**	**479**	**478**	**1343**	**5634**
% APAS < Reference		NA	1.3	2.5	3.0	
% APAS = Reference		98.2	91.9	85.1	97.0	
% APAS > Reference		1.8	6.9	12.3	NA	

Site 2 (ex-US)		Reference Method (CFU/mL)				
		No Growth	**10^3**	**10^4**	**$\geq 10^5$**	**Total**
APAS (CFU/mL)	**No Growth**	1257	2	1	0	**1260**
	10^3	8	168	4	0	**180**
	10^4	0	16	136	8	**160**
	$\geq 10^5$	0	0	13	156	**169**
	Total	**1265**	**186**	**154**	**164**	**1769**
% APAS < Reference		NA	1.1	3.2	4.9	
% APAS = Reference		99.4	90.3	88.3	95.1	
% APAS > Reference		0.6	8.6	8.4	NA	

Site 3 (ex-US)		Reference Method (CFU/mL)				
		No Growth	**10^3**	**10^4**	**$\geq 10^5$**	**Total**
APAS (CFU/mL)	**No Growth**	1241	3	1	0	**1245**
	10^3	2	127	3	0	**132**
	10^4	0	17	115	3	**135**
	$\geq 10^5$	0	0	27	282	**309**
	Total	**1243**	**147**	**146**	**285**	**1821**
% APAS < Reference		NA	2.0	2.7	1.1	
% APAS = Reference		99.8	86.4	78.8	98.9	
% APAS > Reference		0.2	11.6	18.5	NA	

All Sites Combined		Reference Method (CFU/mL)				
		No Growth	**10^3**	**10^4**	**$\geq 10^5$**	**Total**
APAS (CFU/mL)	**No Growth**	5772	11	3	2	**5788**
	10^3	66	735	18	0	**819**
	10^4	4	66	658	49	**777**
	$\geq 10^5$	0	0	99	1741	**1840**
	Total	**5842**	**812**	**778**	**1792**	**9224**
% APAS < Reference		NA	1.4	2.7	2.8	
% APAS = Reference		98.8	90.5	84.6	97.2	
% APAS > Reference		1.2	8.1	12.7	NA	

NA: Not Applicable

Table 24. Correlation of colony count categories obtained by APAS Compact with Urine Analysis Module and the manual reference method (blood agar and MacConkey agar combined)

Site 1 (US)		Reference Method (CFU/mL)				
		No Growth	**10^3**	**10^4**	**$\geq 10^5$**	**Total**
APAS (CFU/mL)	**No Growth**	1166	37	4	0	**1207**
	10^3	276	1059	86	2	**1423**
	10^4	9	178	836	20	**1043**
	$\geq 10^5$	1	6	246	1708	**1961**
	Total	**1452**	**1280**	**1172**	**1730**	**5634**
% APAS < Reference		NA	2.9	7.7	1.3	
% APAS = Reference		80.3	82.7	71.3	98.7	
% APAS > Reference		19.7	14.4	21.0	NA	

Site 2 (ex-US)		Reference Method (CFU/mL)				
		No Growth	**10^3**	**10^4**	**$\geq 10^5$**	**Total**
APAS (CFU/mL)	**No Growth**	429	13	1	0	**443**
	10^3	69	393	32	1	**495**
	10^4	7	64	367	16	**454**
	$\geq 10^5$	0	9	90	278	**377**
	Total	**505**	**479**	**490**	**295**	**1769**
% APAS < Reference		NA	2.7	6.7	5.8	
% APAS = Reference		85.0	82.0	74.9	94.2	
% APAS > Reference		15.0	15.2	18.4	NA	

Site 3 (ex-US)		Reference Method (CFU/mL)				
		No Growth	**10^3**	**10^4**	**$\geq 10^5$**	**Total**
APAS (CFU/mL)	**No Growth**	555	9	2	3	**569**
	10^3	63	326	26	7	**422**
	10^4	0	45	245	12	**302**
	$\geq 10^5$	0	6	108	414	**528**
	Total	**618**	**386**	**381**	**436**	**1821**
% APAS < Reference		NA	2.3	7.3	5.0	
% APAS = Reference		89.8	84.5	64.3	95.0	
% APAS > Reference		10.2	13.2	28.3	NA	

All Sites Combined		Reference Method (CFU/mL)				
		No Growth	**10^3**	**10^4**	**$\geq 10^5$**	**Total**
APAS (CFU/mL)	**No Growth**	2150	59	7	3	**2219**
	10^3	408	1778	144	10	**2340**
	10^4	16	287	1448	48	**1799**
	$\geq 10^5$	1	21	444	2400	**2866**
	Total	**2575**	**2145**	**2043**	**2461**	**9224**
% APAS < Reference		NA	2.8	7.4	2.5	
% APAS = Reference		83.5	82.9	70.9	97.5	
% APAS > Reference		16.5	14.4	21.7	NA	

NA: Not Applicable

b. Clinical specificity:

Refer to **Section 3(a)**, above.

c. Other clinical supportive data (when a. and b. are not applicable):

Not applicable.

4. Clinical cut-off**:**

Not applicable.

5. Expected values/Reference range:

Tables 25-27 show the percentage samples with microbial growth at different levels observed during the clinical studies by the reference method (manual inspection of plates) and by the APAS Compact with Urine Analysis Module. Refer to **Section L(1)(b)** for categorization of colony counts.

Table 25. Percentage of samples with microbial growth at different levels on blood agar as determined by the reference method and APAS Compact with Urine Analysis Module

Category	Percentage of Samples							
	Reference Method [1]				APAS Compact			
	Site 1	Site 2	Site 3	Overall	Site 1	Site 2	Site 3	Overall
No growth	26.4	29.0	35.0	28.6	22.4	25.6	32.2	24.9
10^3 CFU/mL	22.6	26.7	20.4	23.0	24.8	27.6	22.5	24.9
10^4 CFU/mL	20.7	27.6	20.9	22.1	18.5	25.9	16.6	19.6
$\geq 10^5$ CFU/mL	30.2	16.7	23.8	26.3	34.2	20.9	28.7	30.6
Any Growth	73.6	71.0	65.0	71.4	77.6	74.4	67.8	75.1

Site 1: US; Sites 2 and 3: ex-US

[1] Manual review of urine cultures by a panel of microbiologists (refer to **Section L(3)(a)**)

Table 26. Percentage of samples with microbial growth at different levels on MacConkey agar as determined by the reference method and APAS Compact with Urine Analysis Module

Category	Percentage of Samples							
	Reference Method [1]				APAS Compact			
	Site 1	Site 2	Site 3	Overall	Site 1	Site 2	Site 3	Overall
No growth	59.2	71.5	68.3	63.3	58.3	71.2	68.4	62.7
10^3 CFU/mL	8.5	10.5	8.1	8.8	9.0	10.2	7.2	8.9
10^4 CFU/mL	8.5	8.7	8.0	8.4	8.6	9.0	7.4	8.4
$\geq 10^5$ CFU/mL	23.8	9.3	15.7	19.4	24.2	9.6	17.0	19.9
Any Growth	40.8	28.5	31.7	36.7	41.7	28.8	31.6	37.3

Site 1: US; Sites 2 and 3: ex-US

[1] Manual review of urine cultures by a panel of microbiologists (refer to **Section L(3)(a)**)

Table 27. Percentage of samples with microbial growth at different levels on blood agar and MacConkey agar combined as determined by the reference method and APAS Compact with Urine Analysis Module

Category	Percentage of Samples							
	Reference Method [1]				APAS Compact			
	Site 1	Site 2	Site 3	Overall	Site 1	Site 2	Site 3	Overall
No growth	25.8	28.5	33.9	27.9	21.4	25.0	31.2	24.1
10^3 CFU/mL	22.7	27.1	21.2	23.3	25.3	28.0	23.2	25.4
10^4 CFU/mL	20.8	27.7	20.9	22.1	18.5	25.7	16.6	19.5
$\geq 10^5$ CFU/mL	30.7	16.7	23.9	26.7	34.8	21.3	29.0	31.1
Any Growth	74.2	71.5	66.1	72.1	78.6	75.0	68.8	75.9

Site 1: US; Sites 2 and 3: ex-US

[1] Manual review of urine cultures by a panel of microbiologists (refer to **Section L(3)(a)**)

M. Instrument Name:

APAS Compact

N. System Descriptions:

1. Modes of Operation:

   Manual loading/unloading of individual culture plates and image capture, followed by automated analysis and compilation of the test report.

2. Software:

   FDA has reviewed applicant's Hazard Analysis and software development processes for this line of product types:

   Yes ___**X**___ or No _____

   The sponsor provided the results of verification and validation testing for the following software components:

Component Name	Function
Instrument Controller Software	Graphical User Interface (GUI) application that sends and receives messages to and from the APAS Controller.
LIMS Importer Software	GUI application that imports LIMS data and adds it the database that is accessed by the Instrument Controller Software.
APAS Controller Software	Encodes the image processing and assessment algorithms.
Urine Analysis Module Software	Comprised of the Assessment and Decision Packages (AP and DP) which direct the capture and processing of culture plate images, respectively.

3. Specimen Identification:

   Sample identification is entered into the Instrument Controller Software either by typing manually or using a barcode scanner.

4. Specimen Sampling and Handling:

   Culture plates are loaded and unloaded manually, one at a time.

5. Calibration:

   The APAS Compact requires daily color calibration prior to use. Calibration is performed using the Color Calibration Tool provided with the instrument. Instructions for calibration are included in the APAS Compact User Manual.

6. Quality Control:

   Instructions for daily Quality Control testing using reference culture plates inoculated with *Enteroccocus faecalis* and *Escherichia coli* are provided in the User Manual for the Urine Analysis Module. Both the appropriate colony morphology and colony count must be obtained in order for the results of the Quality Control testing to be considered acceptable. Appropriate instructions are provided in the User Manual in the event of control failure.

O. Other Supportive Instrument Performance Characteristics Data Not Covered In The "Performance Characteristics" Section above:

Not applicable.

P. Proposed Labeling:

The labeling is sufficient and satisfies the requirements of 21 CFR parts 801 and 809 as well as the Special Controls for this type of device.

Q. Identified Risks to Health and Identified Mitigations:

Identified Risks to Health	Identified Mitigations
False positive results (i.e., incorrect designation of plates for "Review" or as "Positive")	General controls and special controls: (1), (2), (3), (4), (5), (6), (7)
False negative results (i.e., failure to detect growth and incorrect designation of plates as "Negative")	General controls and special controls: (1), (2), (3), (4), (5), (6), (7)

R. Benefit/Risk Analysis:

Summary	
Summary of the Benefit(s)	The primary benefits of the APAS Compact are to the testing laboratory, rather than directly to the patient. Use of the technology to screen urine cultures will allow laboratories to focus attention on those that exhibit growth and eliminate negative cultures from the workflow, thereby reducing the overall workload. This may have a remote benefit to patients by reducing the time to result for urine cultures that exhibit growth, although this was not evaluated under the current *de novo* submission.
Summary of the Risk(s)	The risks associated with the APAS Compact are the potential for false positive and false negative results. False positive results (i.e., incorrect designation of plates for "Review" or as "Positive") do not appreciably increase the risk of harm to patients because all plates designated as such are required to undergo work-up according to Standard Of Care (SOC) practices. The main consequence of false positive results would therefore be unnecessary expenditure of laboratory resources. False negative results (i.e., failure to detect growth and incorrect designation of plates as "Negative") could lead to the discard of culture plates without further review. In turn this may cause a delay in diagnosis or failure to detect infection and/or under treatment of a UTI. Untreated UTIs can lead to pyelonephritis, renal abscesses, bacteremia and/or urosepsis with increased morbidity and mortality.

Summary	
Conclusions Do the probable benefits outweigh the probable risks?	Yes. There are no benefit-risk considerations that would preclude granting the sponsor's *de novo* application. The probable benefits of the APAS Compact are likely to outweigh the risk in the light of the special controls and applicable general controls, including design controls. The primary risk associated with the APAS Compact is false negative results. False positive results do not substantially increase the risk of harm to patients relative to SOC testing. All plates designated by APAS Compact as "Review" or "Positive" are required to undergo additional evaluation and appropriate work-up by a trained microbiologist according to current SOC practices. APAS Compact results of "Review" or "Positive" would therefore not be reported if the SOC evaluation was "Negative." The performance observed during the clinical studies indicates that the APAS Compact accurately identifies the presence of growth on urine culture plates (overall sensitivity for detection of growth was 99.0% [95% CI: 98.7-99.2%]), and that false negative results are unlikely to occur. The APAS Compact with Urine Analysis Module presents a potential benefit to patients by reducing laboratory turnaround time for culture results for positive specimens, leading to improvements in patient management and more timely administration of appropriate antimicrobial treatment.

Patient Perspectives

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

S. Conclusion:

The information provided in this submission is sufficient to classify this device into Class II under regulation 21 CFR.866.2190. FDA believes that the stated special controls, and applicable general controls, including design controls, provide a reasonable assurance of the safety and effectiveness of the device type. The device is classified under the following:

Product Code: PPU

Device Type: Automated image assessment system for microbial colonies on solid culture media

Class: II (special controls)

Regulation: 21 CFR 866.2190

(a) *Identification.*

An automated image assessment system for microbial colonies on solid culture media is an instrument system that is intended to assess the presence or absence of microbial colonies on solid microbiological culture medium, and to interpret their number, phenotypic and morphologic characteristics through analysis of two dimensional digital images as an aid in diagnosis of infectious disease.

(b) *Classification.*

Class II (special controls). An automated image assessment system for microbial colonies on solid culture media must comply with the following special controls:

1. Pre-market notification submissions must include a detailed description of the device, including the technology employed, components and software modules, as well as a detailed explanation of the result algorithms and any expert rules that are used to assess colony characteristics and enumerate colonies from image capture through end result.

2. Pre-market notification submissions must include detailed documentation of the analytical studies performed to characterize device performance to support the intended use, as appropriate.

3. Pre-market notification submissions must include detailed documentation from clinical studies performed on a population that is consistent with the intended use population.

    i. The clinical studies must establish the device performance based on comparison to results obtained by an acceptable reference method, as appropriate.

    ii. The clinical study documentation must include the study protocol with a predefined statistical analysis plan and the final report documenting support for the Indications for Use and the results of the statistical analysis, as appropriate.

4. Pre-market notification submissions must include detailed documentation for device software, including but not limited to software applications and hardware based components that incorporate software, and any decision making thresholds used to generate results for the device. If a part of a Total Laboratory Automation System, the pre-market notification submission must include detailed documentation addressing the instrument and software system integration.

5. Pre-market notification submissions must include detailed documentation of appropriate instructions for use regarding the intended user's device quality control procedures for the instrument system and components, as appropriate.

6. The 21 CFR 809.10 compliant device labeling must include:

i. Detailed user instructions to mitigate the risk of failure to operate the instrument correctly.

ii. A detailed explanation of the interpretation of results and limitations regarding the need for review of culture plates by a qualified microbiologist, as appropriate.

iii. A summary of performance data obtained from the analytical studies used to support device performance, as appropriate.

iv. A summary of performance data obtained from clinical studies performed on a population that is consistent with the intended use population, as appropriate.

7. Under 21 CFR 820.30 compliant design control, device manufacturers must, as appropriate:

    i. Conduct human factors/usability validation testing with the final version of the labeling and related materials to adequately mitigate the risk of failure to operate the instrument correctly.

    ii. Document a device training program that will be offered to the end user to adequately mitigate the risk of failure to operate the instrument correctly.