May 15, 2019

Clever Culture Systems AG
Julie Winson
Regulatory Affairs Manager
Seestrasse 204a
Bach, CH-8806 CH

Re: K183648
Trade/Device Name: APAS Independence with Urine Analysis Module
Regulation Number: 21 CFR 866.2190
Regulation Name: Automated Image Assessment System For Microbial Colonies On Solid Culture Media
Regulatory Class: Class II
Product Code: PPU
Dated: December 20, 2018
Received: December 26, 2018

Dear Julie Winson:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database located at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm identifies combination product submissions. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's

requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801 and Part 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803) for devices or postmarketing safety reporting (21 CFR 4, Subpart B) for combination products (see https://www.fda.gov/CombinationProducts/GuidanceRegulatoryInformation/ucm597488.htm); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/) and CDRH Learn (http://www.fda.gov/Training/CDRHLearn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (http://www.fda.gov/DICE) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

for

Uwe Scherf, M.Sc., Ph.D.
Director
Division of Microbiology Devices
OHT7: Office of In Vitro Diagnostics
and Radiological Health
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

Enclosure

5. 510(k) Summary

510(k) Number: K183648

5.1 Submitter

Clever Culture Systems AG
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Switzerland

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Date prepared: 8th May 2019

5.2 Device

Name of Device: APAS Independence with Urine Analysis Module.

Common or usual name: APAS Independence.

Classification name: Automated image assessment system for microbial colonies on solid culture media (21 CFR 866.2190).

Regulatory Class: II (special controls).

Product Code: PPU.

5.3 Predicate Device

APAS Compact with Urine Analysis Module, DEN150059.

This predicate has not been subject to a design related recall.

No reference devices were used in this submission.

5.4 Device Description

APAS Independence with Urine Analysis Module is a device designed to be used in a microbiology laboratory to automate the initial screening for the presence of growth on urine culture plates. It is an *in vitro* diagnostic device and has no direct contact with patients.

APAS Independence consists of an automated plate handling mechanism to move the plates through the instrument, an imaging station to capture an image of the culture plate, combined with software for analysis of the image, determination of growth and presentation of reports.

The APAS Independence with Urine Analysis Module is intended to determine whether growth is present or not, and to provide a semi-quantitative assessment of the colony count (if present). This information will then be combined with other available clinical information to screen out biological samples without growth. All other plates will be presented to a microbiologist for examination, determination of status and further testing according to conventional laboratory practice. This enables the microbiologist to focus on plates with potentially significant growth, thereby reducing the time until results can be reported.

The APAS Independence is intended to have different software modules, each of which will provide an assessment of growth for specific clinical indications. This submission covers only the APAS Independence with Urine Analysis Module. The APAS Independence with Urine Analysis Module is indicated for screening of culture plates for assessment of urinary tract infections where the urine specimens are collected and 1µl is plated onto Blood and MacConkey Agars and incubated at 35±2°C for 18 to 22 hours.

Figure 5.1 shows a photograph of the instrument from the front. It shows the input area on the left, the imaging area in the middle and the output area on the right. The user controls the instrument via the screen at the top middle of the instrument.

Figure 5.1 – APAS Independence

Figure 5.2 provides a logical connection diagram of the components that make up the complete system (the hatched components are not part of the predicate device).

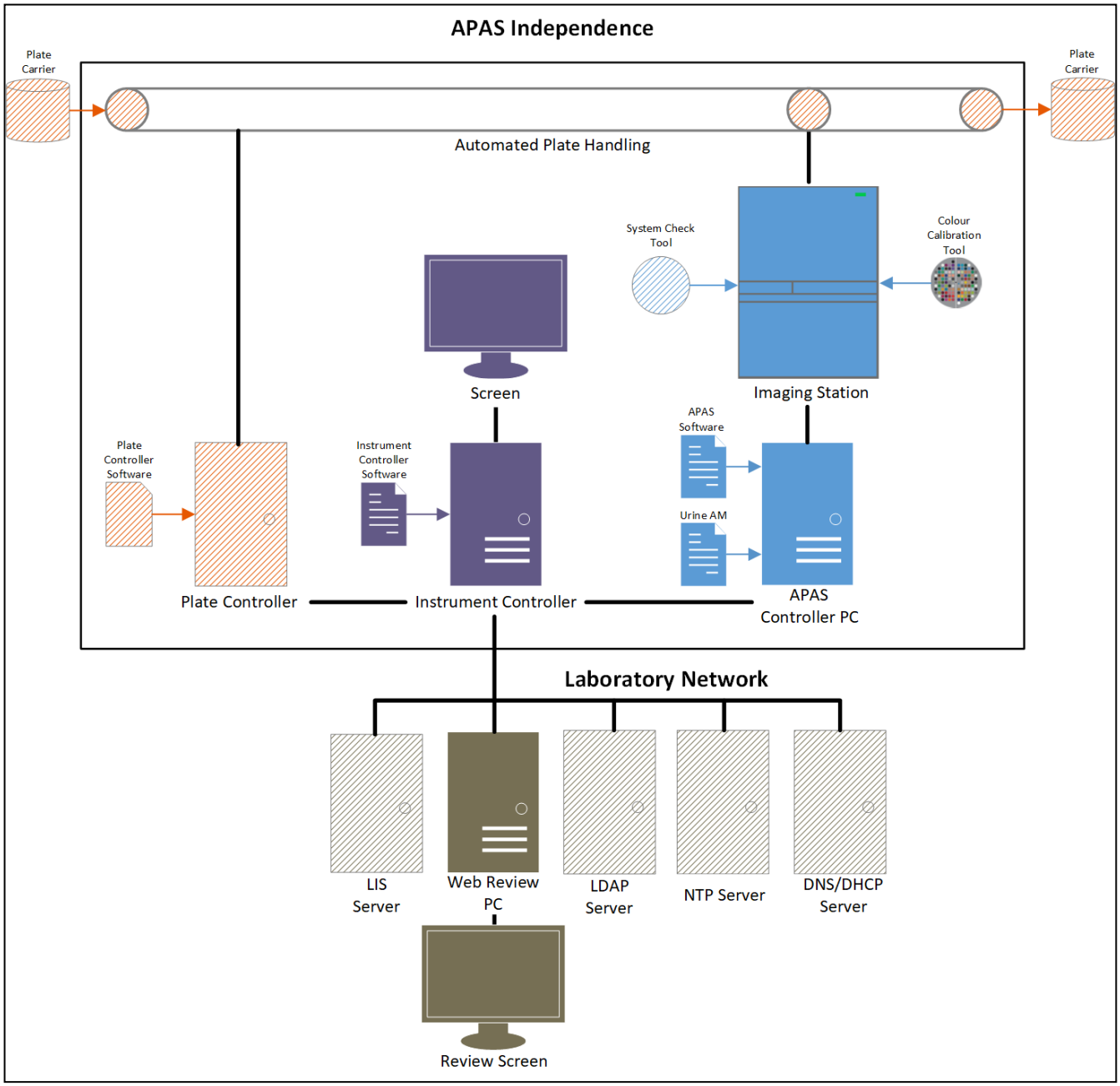

Figure 5.2 – The APAS Independence with Urine Analysis Module

The major sub-systems within the APAS Independence are:

- Imaging Station;
- APAS Controller;
- Instrument Controller;
- Plate Controller;
- Automated plate handling.

The additional components supplied with the system are shown in Table 5.1.

Sub-system	Includes	Description
APAS Independence	Four-stack Carriers	Used to transport approximately sixty plates to and from the instrument
	Single-stack Carriers	Used to transport approximately twenty plates to and from the instrument
	Color Calibration Tool	Used to calibrate and check the color response of the imaging system
	System Check Tool	Used to perform a quick end-to-end check of the instrument hardware and software
	User Manual	Provides instructions for use of the instrument
	User Training Material	Provides training details on the use of the instrument
	Service Manual	Provides instructions for the servicing of the instrument
Urine Analysis Module	Installer	The software to be installed on an APAS Independence instrument
	User Manual	Provides instructions for use of the Analysis Manual
	User Training Material	Provides training details on the use of the Analysis Module

Table 5.1 – System Components

5.5 Intended Use

The APAS Independence is an *in vitro* diagnostic system comprised of an instrument and software analysis module(s) for specific indications that are used to automate imaging and interpretation of microbial colonies on plates of solid culture media.

5.6 Indications for Use

The APAS Independence 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 Independence, 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 Independence, 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 Independence, when using its urine analysis module, must be reviewed by a trained microbiologist.

5.7 Comparison of Technological Characteristics with the Predicate Device

The nominated predicate device is APAS Compact with Urine Analysis Module, which was cleared via *de novo* DEN150059.

APAS Independence adds automated plate handling to the existing functionality of automated plate interpretation within APAS Compact.

The two devices have the same Intended Use and same Indications for Use and use the same technology to provide an interpretation of growth from urine cultures as an aid in the diagnosis of urinary tract infection.

Both devices have been developed by Clever Culture Systems (CCS).

Table 5.2 below provides a side-by-side comparison of the main characteristics of the two devices.

Characteristic	Commonalities	Differences	Comments
Intended Use	Same	Change of device name from Compact to Independence	
Indications for Use	Same	Change of device name from Compact to Independence	
Target population	All patients suspected of urinary tract infection who submit urine specimens for culture	None	
Anatomical site	Urine samples	None	
Where used	Microbiology laboratory	None	
Standards met	IEC 61010-1: 2010 (3rd ed) IEC 61326-1: 2012 IEC 61326-2-6: 2012 EN 55011: 2009/A1:2010 CISPR-11: 2010 FCC 15B ISO 14971: 2007 IEC 62304: 2006	The subject device also meets: UL 61010-1 (3rd ed), rev 2015-07 IEC 61010-2-101: 2015 IEC 62366-1: 2015	The predicate was tested against the safety and EMC/EMI standards that were relevant for that device. The subject device has been tested against the same standards but also the UL version of the 61010 standard and the IVD specific sub-standard in that family. Usability engineering has followed IEC 62366-1 for the subject device in addition to the FDA guidelines.
Electrical safety	IEC 61010-1: 2010 (3rd ed)	The subject device also meets: UL 61010-1 (3rd ed), rev 2015-07 IEC 61010-2-101: 2015	
Mechanical safety	IEC 61010-1: 2010 (3rd ed)	The subject device also meets: UL 61010-1 (3rd ed), rev 2015-07 IEC 61010-2-101: 2015	
Chemical safety	No exposure to chemical substances	None	
Thermal safety	IEC 61010-1: 2010 (3rd ed)	The subject device also meets: UL 61010-1 (3rd ed), rev 2015-07 IEC 61010-2-101: 2015	
Radiation safety	LED lights Barcode scanner	In the subject device, the imaging station is closed to operators during processing and barcode reading is enclosed within the instrument	
Energy used and/or delivered	Imaging station powered from 24VDC. APAS Controller and Instrument Controller PCs power from standard ATX supplies	The subject device has an automated plate handling system powered from 24VDC.	The subject device is the same as the predicate device in that it uses 24VDC rather than AC mains for all possible areas of the instrument including all operator accessible areas.

Characteristic	Commonalities	Differences	Comments
Materials	General engineering plastics and metals	None	
Biocompatibility	No body contact	None	
Compatibility with the environment and other devices	IEC 61326-1: 2012 IEC 61326-2-6: 2012 EN 55011: 2009/A1:2010 CISPR-11: 2010 FCC 15B	None	
Sterility	Not a sterile device	None	

Table 5.2– Comparison of Characteristics Between Predicate and New Device

5.8 Performance Data

The following performance data were provided in support of the substantial equivalence determination.

5.8.1 Safety and EMC

Electrical safety and EMC testing were conducted on the subject device, consisting of the instrument, carriers and qualification tools. The system complies with IEC 61010-1: 2010, IEC 61010-2-101: 2017 and UL 61010-1: 2012 for safety and IEC 61326-1: 2013, IEC 61326-2-6: 2013 and FCC Part 15B for EMC.

5.8.2 Software Verification and Validation

Software verification and validation testing were conducted, and documentation was provided as recommended by FDA's Guidance for Industry and Staff, *Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices*. The software for this device was considered as a "moderate" level of concern as a malfunction of, or latent design flaw in the software could lead to an erroneous diagnosis or a delay in delivery of appropriate medical care that would likely lead to a Minor injury to the patient.

5.8.3 Clinical Studies

The predicate device, APAS Compact with Urine Analysis Module and the new device, APAS Independence with Urine Analysis Module both utilize the same core APAS technology and the same urine analysis module to image culture plates and read and interpret growth.

Therefore, the clinical performance of the predicate device represents the clinical performance of the new device, APAS Independence with Urine Analysis Module.

The results of three clinical studies (LBT001, LBT002 and LBT003) were submitted to support the *de novo* application DEN150059 and showed that APAS performed similarly to a microbiologist in reading and interpreting agar plates cultured for screening for uncomplicated urinary tract infection (UTI).

A confirmatory Method Comparison Study between the APAS Independence and APAS Compact was performed using 350 leftover clinical urine samples that were accepted for screening for UTI. 1µL of each urine sample was inoculated onto each of a pair of blood and MacConkey agar plates and incubated at 35±2°C for 18 hr. The plates were read by both APAS Compact and APAS Independence with the same urine analysis module and the results compared.

The APAS Compact and APAS Independence provided a screening result of the sample on each agar of either Positive, Review or Negative. A 3x3 confusion matrix is provided for blood and MacConkey agar in Table 5.3**.** and Table 5.4, respectively.

Table 5.3 shows that when APAS Compact reported a Positive result on blood agar, APAS Independence either agreed or returned a Review result. There were no cases where APAS Independence returned a Negative result and which therefore would not be looked at by a microbiologist. For those samples originally classified as Negative by APAS Compact, APAS Independence either agreed or assigned a Review and Positive designation which requires investigation by a microbiologist. The results indicate that on blood agar, there is a high level of agreement between APAS Independence and APAS Compact and that APAS Independence is slightly more likely than APAS Compact to assign a Positive or Review result (288 cases for APAS Independence compared with 272 cases for APAS Compact).

Table 5.3: Plate designation for blood agar: APAS Compact (predicate) vs APAS Independence with Urine Analysis Module

<table>
<tr><th colspan="2" rowspan="2">Blood Agar
Plate Designation</th><th colspan="4">APAS Compact (predicate)</th></tr>
<tr><th>Positive</th><th>Review</th><th>Negative</th><th>Total</th></tr>
<tr><td rowspan="4">APAS Independence</td><td>Positive</td><td>232</td><td>5</td><td>1</td><td>238</td></tr>
<tr><td>Review</td><td>3</td><td>32</td><td>15</td><td>50</td></tr>
<tr><td>Negative</td><td>0</td><td>0</td><td>62</td><td>62</td></tr>
<tr><td>Total</td><td>235</td><td>37</td><td>78</td><td>350</td></tr>
<tr><td colspan="2" rowspan="2">Designation Agreement
(95% Confidence Interval)</td><td>232/235
98.7%
(96.3-99.6%)</td><td>32/37
86.5%
(72.0-94.1%)</td><td rowspan="2">62/78
79.5%
(69.2-87.0%)</td><td rowspan="2"></td></tr>
<tr><td colspan="2">272/272
100% [1]
(98.6-100%)</td></tr>
</table>

[1] "Positive" and "Review" designations combined

The results for MacConkey agar in Table 5.4 follow a similar pattern. When APAS Compact reported a Positive result, APAS Independence agreed, with the exception of a single sample that was reported as Negative by APAS Independence. For those samples originally classified as Negative by APAS Compact, APAS Independence either agreed or assigned a Review and Positive designation which requires investigation by a microbiologist. The results indicate that on MacConkey agar, there is a high level of agreement between APAS Independence and APAS Compact and that APAS Independence is more likely than APAS Compact to assign a Positive or Review result (161 cases for APAS Independence compared with 139 cases for APAS Compact).

Table 5.4: Plate designation for MacConkey agar: APAS Compact (predicate) vs APAS Independence with Urine Analysis Module

MacConkey Agar Plate Designation		**APAS Compact (predicate)**			
		Positive	**Review**	**Negative**	**Total**
APAS Independence	**Positive**	133	1	8	**142**
	Review	0	4	15	**19**
	Negative	1	0	188	**189**
	Total	**134**	**5**	**211**	**350**
Designation Agreement (95% Confidence Interval)		133/134 **99.3%** (95.9-99.9%)	4/5 **80.0%** (37.6-96.4%)	188/211 **89.1%** (84.2-92.6%)	
		137/139 **98.6%** [1] (94.9-99.6%)			

[1] "Positive" and "Review" designations combined

The findings for plate designation are supported by comparative data for agreement of colony counts presented in Table 5.6 for blood agar and Table 5.7 for MacConkey agar, which demonstrate that for both agars, while overall there was a high level of agreement between the two systems, APAS Independence was more likely to overestimate than underestimate enumeration. This is acceptable because all plates with growth are subject to additional follow-up by a trained microbiologist and there is no increased risk to patients.

Table 5.5: Colony counts on blood agar obtained with the Urine Analysis Module using the APAS Compact (predicate) and APAS Independence

Colony Counts on Blood Agar		**APAS Compact CFU/mL (predicate)**					
		0	**10^3**	**10^4**	**10^5**	**IND**	**Total**
APAS Independence CFU/mL	**0**	62	0	0	0	0	**62**
	10^3	15	47	0	0	0	**62**
	10^4	1	5	67	1	0	**74**
	10^5	0	0	7	132	0	**139**
	IND	0	0	0	0	13	**13**
	Total	**78**	**52**	**74**	**133**	**13**	**350**
% Independence < Compact		**NA**	**0**	**0**	**0.8**	**NA**	
% Independence = Compact		**79.5**	**90.4**	**90.5**	**99.2**	**100**	
% Independence > Compact		**20.5**	**9.6**	**9.5**	**NA**	**NA**	

IND: Indeterminate (swarming organism)

Table 5.6: Colony counts on MacConkey agar obtained with the Urine Analysis Module using the APAS Compact (predicate) and APAS Independence

Colony Counts on MacConkey Agar		APAS Compact CFU/mL (predicate)				
		0	**10^3**	**10^4**	**10^5**	**Total**
APAS Independence CFU/mL	**0**	188	1 [1]	0	0	**189**
	10^3	15	26	0	0	**41**
	10^4	8	2	21	0	**31**
	10^5	0	0	3	86	**89**
	Total	**211**	**29**	**24**	**86**	**350**
% Independence < Compact		**NA**	**3.4**	**0**	**0**	
% Independence = Compact		**89.1**	**89.7**	**87.5**	**100**	
% Independence > Compact		**10.9**	**6.9**	**12.5**	**NA**	

[1] APAS Compact detected a single lactose fermenting colony that was not identified by APAS Independence

The test also compared colony morphology detection between paired sample plate images assessed by APAS Compact and APAS Independence. The results are presented in Table 5.7 for blood agar and Table 5.8 for MacConkey agar.

The results demonstrate a probability of >95% detection across all colony types. In general, the APAS Independence is likely to overestimate some colony morphologies (AC-/AI+ > AC+/AI-).

The columns in the tables are;

Colony Morphology	denotes the target colony morphologies
AC+/AI+	means that the colony morphology was detected by **both** APAS Compact (AC) and APAS Independence (AI).
AC+/AI-	means that the colony morphology was detected by APAS Compact but not by APAS Independence [ie false negative]
AC-/AI+	means that the colony morphology was not detected by APAS Compact but was detected by APAS Independence [ie false positive]
AC- / AI-	means that the colony morphology was not detected by either instrument
Equiv (Equivalent)	is the number of plates where the colony morphology was; detected by both instruments, or not detected by both instruments, or detected by APAS Independence only.[1]
Percent	is the proportion calculated as Equivalent divided by the Cases, with 95% confidence intervals calculated using the Wilson score method.

[1] Detection by APAS Independence only was considered acceptable and included in the equivalence calculation because all plates with growth are subject to additional follow-up by a trained microbiologist and there is no additional risk to the patient

Table 5.7: APAS Independence detection of colony morphologies compared to APAS Compact detection of colony morphologies on TS-SBA agar

Colony morphology	Present APAS Compact		Not Present APAS Compact		Cases	Equiv	Percent (95% confidence interval)
	AC+/AI+	AC+/AI-	AC-/AI+	AC-/AI-			
Alpha hemolysis	61	10	43	236	350	340	0.971 (0.948, 0.984)
Beta hemolysis	106	13	38	193	350	337	0.963 (0.937, 0.978)
Coliform	165	4	13	168	350	346	0.989 (0.971, 0.996)
Cream white	176	17	12	145	350	333	0.951 (0.924, 0.969)
Granular	18	1	1	330	350	349	0.997 (0.984, 0.999)
Small	195	6	44	105	350	344	0.983 (0.963, 0.992)
Swarming	13	0	0	337	350	350	1.000 (0.989, 1.000)

Table 5.8: APAS Independence detection of colony morphologies compared to APAS Compact detection of colony morphologies on MacConkey agar

Colony morphology (PIC)	Present APAS Compact		Not Present APAS Compact		Cases	Equiv	Percent (95% confidence interval)
	AC+/AI+	AC+/AI-	AC-/AI+	AC-/AI-			
Lactose fermenter	110	3	1	236	350	347	0.991 (0.975, 0.997)
Non-fermenter	51	2	33	264	350	348	0.994 (0.979, 0.998)
Non-pigmented	1	0	0	349	350	350	1.000 (0.989, 1.000)
Red Pink	7	0	13	330	350	350	1.000 (0.989, 1.000)

5.8.4 Reproducibility & Precision

A study was performed using three APAS Independence instruments equipped with a Urine Analysis Module to show that the extent of variability in colony counts within and between these instruments is equivalent to that found with APAS Compact with Urine Analysis Module. The test was conducted using three dilutions of cultured organisms which were selected as being representative of those found in urine samples. The organisms used on blood agar were E. coli, Streptococcus agalactiae and Enterococcus faecalis. The organism used on MacConkey agar was E. coli. The test included blank plates inoculated with sterile saline. 1µL from a dilution of an organism representing 10^3 CFU/mL, 10^4 CFU/mL or 10^5 CFU/mL was inoculated onto one of 3 replicates per dilution and incubated for 35°C ± 2°C for 18 hrs. Each culture plate was imaged five times at three different orientations within each of the three instruments and the resulting colony counts per plate were compared to determine the repeatability of colony count as a percent coefficient of variation (%CV) within an instrument, and reproducibility of colony count as a %CV across instruments. The results are shown in Table 5.9.

Table 5.9: Collation of %CV values obtained by the APAS Independence with Urine Analysis Module

Agar	Species	Lowest Dilution (>100 CFU/mL)				Middle Dilution (10-99 CFU/mL)				Highest Dilution (1-9 CFU/mL)			
		APAS 1	APAS2	APAS3	ALL APAS	APAS 1	APAS2	APAS3	ALL APAS	APAS 1	APAS2	APAS3	ALL APAS
MacConkey	E coli	4.4	1.9	3.0	7.2	5.4	3.0	4.5	5.6	14.0	24.6	13.6	21.7
	Saline	0.0	0.0	0.0	0.0								
TS-SBA	E coli	1.7	7.9	2.0	5.0	2.3	3.0	3.0	6.7	14.7	22.6	10.1	20.4
	E coli / Strep	4.7	3.7	9.2	10.0	6.0	6.2	16.3	12.3	22.6	26.3	25.1	28.1
	E faecalis	5.7	4.0	2.2	7.4	7.5	5.9	5.4	11.6	22.4	19.3	27.6	27.7
	Saline	0.0	0.0	0.0	0.0								

As noted with APAS Compact with Urine Analysis Module, the value for %CV is inversely proportional to colony count. Overall, the reproducibility and precision of colony counts with the APAS Independence with Urine Analysis Module was similar to that of observed with the APAS Compact with Urine Analysis Module and was therefore acceptable.

5.9 Conclusions

The predicate device, APAS Compact with Urine Analysis Module and the new device, APAS Independence with Urine Analysis Module both utilize the same core APAS technology and the same urine analysis module to image culture plates and read and interpret growth.

The non-clinical data support the safety of the device and the hardware and software verification and validation demonstrate that the subject device should perform as intended in the specified use conditions. The equivalence study confirms that the two devices return the same clinical result. The results obtained with the new device also demonstrated acceptable reproducibility and precision.

Therefore, the data demonstrate that the subject device is substantially equivalent to the predicate device.