March 5, 2020

SSI Diagnostica A/S
% Christopher Bentsen
Regulatory and Clinicals Consultant
Bentsen Regulatory and Clinicals Consulting LLC
25803 NE 9th Street
Redmond, Washington 98074

Re: K191184
Trade/Device Name: ImmuView S pneumoniae and L pneumophila Urinary Antigen Test
Regulation Number: 21 CFR 866.3300
Regulation Name: Haemophilus Spp. Serological Reagents
Regulatory Class: Class II
Product Code: MJH, GTZ
Dated: June 3, 2019
Received: June 10, 2019

Dear Christopher Bentsen:

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/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products); 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 https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance) and CDRH Learn (https://www.fda.gov/training-and-continuing-education/cdrh-learn). 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 (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

Kristian Roth, Ph.D.
Chief
Bacterial Multiplex and Medical Counter Measures Branch
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

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: 06/30/2020
See PRA Statement below.

510(k) Number *(if known)*
k191184

Device Name
ImmuView S. pneumoniae and L. pneumophila Urinary Antigen Test

Indications for Use *(Describe)*
Intended use
The ImmuView S. pneumoniae and L. pneumophila Urinary Antigen Test is an in vitro, rapid, lateral flow test, also known as a lateral flow immunochromatographic assay, intended for the qualitative detection of Streptococcus pneumoniae and Legionella pneumophila antigens in urine specimens from patients with symptoms of pneumonia. The assay is intended to aid in diagnosis of S. pneumoniae and L. pneumophila serogroup 1 infections. The assay is further intended to aid in the diagnosis of S. pneumoniae infections by detection of S. pneumoniae antigen in cerebrospinal fluid (CSF). Results from the ImmuView S. pneumoniae and L. pneumophila Urinary Antigen Test should be interpreted in conjunction with the patient's clinical evaluation and other diagnostic methods.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

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510(k) SUMMARY

510(k) # _____k191184_____ Date of Preparation: March 4, 2020

Submitter:	Christopher Bentsen, M.S., RAC, FRAPS; Bentsen Regulatory and Clinicals Consulting LLC.
Submitters Address:	Gig Harbor, Washington 98332
Submitters Number:	(206) 910-1974
Sponsor:	SSI Diagnostica A/S (SSID)
Contact:	Dr. Pernille Landsbo Elverdal, VP R&D
Contact Number:	0045 4111 2731
Device Name:	ImmuView *S. pneumoniae* and *L. pneumophila* Urinary Antigen Test
Common Name:	Urinary Antigen Test, *Streptococcus pneumoniae* and *Legionella pneumophila* serogroup 1
Classification:	*Streptococcus* spp and *Legionella* spp serological reagents 21 CFR 866.3740 and 866.3300
Product Codes:	GTZ and MJH
Predicate Devices:	BinaxNOW® *Streptococcus pneumoniae* (K012521) and BinaxNOW® *Legionella* (K982238)

Panel:

Microbiology

Intended Use:

The ImmuView *S. pneumoniae* and *L. pneumophila* Urinary Antigen Test is an in vitro, rapid, lateral flow test, also known as a lateral flow immunochromatographic assay, intended for the qualitative detection of *Streptococcus pneumoniae* and *Legionella pneumophila* antigens in urine specimens from patients with symptoms of pneumonia. The assay is intended to aid in diagnosis of *S. pneumoniae* and *L. pneumophila* serogroup 1 infections. The assay is further intended to aid in the diagnosis of *S. pneumoniae* infections by detection of *S. pneumoniae* antigen in cerebrospinal fluid (CSF). Results from the ImmuView *S. pneumoniae* and *L. pneumophila* Urinary Antigen Test should be interpreted in conjunction with the patient's clinical evaluation and other diagnostic methods.

Indication(s) for use:

Same as Intended Use

Special conditions for use statement(s):

This device is for *in vitro* diagnostic use only. It is for prescription use only and to be used only by clinical laboratory professionals.

Special instrument requirements:

N/A

Device Description:

ImmuView *S. pneumoniae* and *L. pneumophila* Urinary Antigen Test is a rapid lateral flow test for qualitative detection of *S. pneumoniae* in human urine and CSF samples and *L. pneumophila* (primarily serogroup 1) antigens in human urine samples. The test is effective in presumptive diagnosis of pneumococcal pneumonia caused by *S. pneumoniae* or *Legionella* pneumonia (Legionnaires' disease) caused by *L. pneumophila*, in conjunction with culture and other methods. Correct and early treatment is vital for the prognosis of both diseases and therefore quick methods to confirm both diseases in the initial phase are very important in order to initiate the proper antibiotic treatment as soon as possible.

Substantial Equivalence Information:

1. Predicate device names(s):
   BinaxNOW® *Streptococcus pneumoniae* Card and BinaxNOW® *Legionella pneumophila* Card
2. Predicate 510(k) number(s):
   K991726 and K012521 and K982238 and K070522

Table 1 Comparison with predicate:

Description	ImmuView *S. pneumoniae* and *L. pneumophila* Urinary Antigen Test	BinaxNOW® *Streptococcus pneumoniae* and BinaxNOW® Legionella Antigen Cards
Test Format	Rapid immunochromatographic lateral flow test	Rapid immunochromatographic card tests
Quantitative/Quantitative	Qualitative	Qualitative
Test Antigen	*Streptococcus pneumoniae* and *Legionella pneumophila* serogroup 1	*Streptococcus pneumoniae* or *Legionella pneumophila* serogroup 1
Specimen Types	Human CSF and human urine	Human CSF and human urine
Reagents/Components	Test Strips Test Tubes Sample Running Buffer Negative Control Positive Control Plastic transfer pipettes Tweezer Cardboard test tube holder	Test Cards Reagent A Positive Control Swab Negative Control Swab Swabs
Antibody Sources		
Test Card	Rabbit Polyclonal antibodies	Rabbit Polyclonal antibodies
Conjugate	Rabbit Polyclonal antibodies	Rabbit Polyclonal antibodies
Sample Preparation		
Unpreserved and preserved urine	Add 3 (120 ul) drops of urine or add 10 ul of CSF to a test tube Add 2 (90 ul) drops of sample running diluent Mix well Add test strip with arrow down	1. Dip swab into the urine sample and then insert swab into the bottom hole of the Test Card. 2. Add 2 drops of Reagent A to the bottom hole for Legionella Card and 3 drops for *S. pneumoniae* Card.
Testing Time	Approximately 15 minutes	Approximately 15 minutes
Equipment		
General Laboratory Equipment	Urine collection container Timer Vortex or mix by swirling Disposable gloves	Urine collection container Timer Swab pack Disposable gloves
Reading Method	Visual	Visual
Results Interpretation		
Visual Read	Negative: A single purple/gray Control line in the top of the strip.	Negative: Single pink to purple colored Control line visible in top half of the window
	Positive: For both S. pn. and L. pn. S-1 will show a pink/red line and a blue line. For S. pn. will show a pink/red line. For L. pn. S-1 will show a blue line.	Positive: Two pink to purple lines

	Invalid: No line at the Control line position and if there is a dot instead of a test line. Also, if gray lines appear. Follow IFU instructions	Invalid: No line at the Control line position or no lines at the Control and Sample line positions.	**Test**

Principle:

ImmuView® S. pneumoniae and L. pneumophila Urinary Antigen Test is a rapid lateral flow test for detection of S. pneumoniae and L. pneumophila using the same test.

Clinical Sensitivity and Specificity for Urine Samples (Retrospective study)

To determine the sensitivity of the ImmuView *S. pneumoniae* and *L. pneumophila* Urinary Antigen Test, 100 frozen urine samples from patients originally determined to be infected with ***S. pneumoniae*** were tested. All 100 urine samples came from Europe, and all were from blood culture positive patients; Forty-eight (48) samples were from Sweden[3] and fifty-two (52) samples were from Denmark.

To determine the sensitivity of the ImmuView *S. pneumoniae* and *L. pneumophila* Urinary Antigen Test, 98 stored frozen urine samples from patients with a culture confirmed ***Legionella*** infection were tested. A total of 55 urine samples came from Europe. The remaining 43 urine samples came from the United States (U.S.), and these were also determined to be previously positive in a urinary antigen test.

The clinical specificity of the ImmuView *S. pneumoniae* and *L. pneumophila* test lines was obtained by testing **known negative** (culture confirmed negative) urine samples collected from 3 sites, one in the U.S. and two in Europe.

Table 1

***S. pneumoniae* culture verified vs. ImmuView**		
	Culture positive	Culture negative
ImmuView pos	78	4
ImmuView neg	22	217
Total	100	221
ImmuView Sensitivity	78%	95%CI (69.0-85.0%)
ImmuView Specificity	98.1%	95%CI (95.4-99.3%)
***L. pneumophila* culture verified vs. ImmuView**		
	Culture positive	Culture negative
ImmuView pos	86	1
ImmuView neg	12	239
Total	98	240
ImmuView Sensitivity	87.8%	95%CI (79.8-92.9%)
ImmuView Specificity	99.6%	95%CI (97.7-99.9%)

Table 2

Table 3

Sensitivity (Urine) Based on culture vs comparator		
	ImmuView	Comparator
S. pneumoniae (Blood culture only)	78% (78/100) (CI 67-85%)	80% (76/95[a]) (CI 71-87%)
L. pneumophila Sg 1 (U.S.)	97.7% (42/43) (CI 88-100%)	100% (43/43) (CI 92-100%)
L. pneumophila Sg 1 (Europe)	80.0% (44/55) (CI 68-88%)	66.7% (36/54[b]) (CI 53-78%)
Specificity (Urine) Based on culture vs comparator		
	ImmuView	Comparator
S. pneumoniae (Europe)	98.2% (217/221[c]) (CI 95-99%)	97.8% (218/223) (CI 95-99%)
L. pneumophila (U.S.)	100% (19/19) (CI 83-100%)	100% (19/19) (CI 83-100%)
L. pneumophila (Europe)	99.5% (220/221[d]) (CI 97-100%)	99.6% (223/224) (CI 98-100%)

[a] 5 samples were QNS for testing, [b] 1 sample was QNS for testing, [c] 3 samples were QNS for testing, [d] 3 samples were QNS for testing

S. pneumoniae sensitivity (Europe) increased to 81/100 or 81% for ImmuView *S. pneumoniae* and *L. pneumophila* urinary antigen test compared with comparator that after boiling had 76/95 or 80%. *L. pneumophila* sensitivity (Europe) changed to 41/55 or 74.6% for ImmuView and remained 36/54 or 66.7% for the comparator. The specificity (Europe) increased to 98.6% (218/221) and 100% (221/221) for *S. pneumoniae* and *L. pneumophila* respectively after boiling when using ImmuView. The comparator did not change after boiling. *L. pneumophila* sensitivity (U.S.) increased to 43/43 or 100% (95%CI 91.8-100%) in the ImmuView Test for *L. pneumophila* after boiling[1,2]. *L. pneumophila* specificity (U.S.) did not change after boiling for either test.

Positive and Negative Percent Agreement for urine samples

(Prospective study)

In a prospective study three-hundred-six (306) prospective collected urine samples from two different sites (Spain and Denmark) were tested with both the ImmuView *S. pneumoniae* and *L. pneumophila* Urinary Antigen Test and the Comparator tests. Fresh* urine samples were from patients (all comers) at risk of having community acquired pneumonia. The results were compared with other lateral flow urine antigen tests (Comparator).

Table 4

Prospective samples positive agreement *S. pneumoniae*			
ImmuView	Comparator positive	Comparator negative	Total
Positive	72	6	78
Negative	3	225	228
Total	75	231	306
Positive percent agreement	96.0%	95% CI (88.9%-98.6%)	
Negative percent agreement	97.4%	95% CI (94.5%-98.8%)	
Prospective samples positive agreement *L. pneumophila* SG1			
ImmuView	Comparator positive	Comparator negative	Total
Positive	3	0	3
Negative	0	303	303
Total	3	303	306
Positive percent agreement	100.0%	95% CI (43.9%-100%)	
Negative percent agreement	100.0%	95% CI (98.8%-100%)	

* Of the 306 samples, a total of 92 had to be frozen before testing could be performed.

The positive agreement for *S. pneumoniae* was 72/75 or 96% (88.9-98.6%). The negative agreement for S. pneumoniae was 226/232 or 97.4% (94.5-98.8). The positive agreement for *L. pneumophila* was 3/3 or 100% (43.9-100%). Negative agreement for L. pneumophila was 304/304 or 100% (98.8-100%).

After boiling[1,2] the positive and negative agreement for *S. pneumoniae* and *L. pneumophila* remained the same.

Analytical Studies - Urine

Specificity (Cross-Reactivity)

To determine the analytical specificity of the ImmuView *S. pneumoniae* and *L. pneumophila* Urinary Antigen test for cross-reactivity with urines spiked with whole cell bacteria and different inactivated viruses (N=143). The whole cell bacterial panel was tested in a 10^7 CFU/mL diluted from a stock solution. The Viral panel had a concentration of 10^5 TCID50/mL. The panel was also tested in negative urine.

Table 5

Organisms tested for interference	
Acinetobacter ssp.(4)	*Lactobacillus sp.*
Bacillus subtilis	*Listeria monocytogenes*
Bordetella pertussis	*Morganella morganii*
Moraxella catarrhalis	*Moraxella osloensis*
Candida albicans (4)	*Mycoplasma genitalium*
Citrobacter freundii	*Neisseria gonorrhoeae (3)*
Cornyebacterium sp.	*Neisseria lactamica*
Cornyebacterium uralyticum	*Neisseria meningitidis*
Enterobacter cloacae (3)	*Neisseria polysaccharea*
Escherichia coli (10)	*Proteus mirabilis (2)*
Enterococcus faecalis (7)	*Proteus vulgaris*
Enterococcus faecium	*Pseudomonas aeruginosa (4)*
Enterococcus durans	*Pseudomonas stutzeri*
Gardnerella vaginalis	*Pseudomonas spp. (2)*
Haemophilus Influenzae type a-f and non-caps (11)	*Salmonella bredeney*
Haemophilus paraInfluenzae	*Salmonella Thompson*
Adenovirus 2,	*Salmonella typhimurium*
Chlamydophila pneumoniae (2)	*Serratia marcescens*
Chlamydia trachomatis	*Staphylococcus epidermidis*
Cytomegalovirus	*Salmonella glostrup*
Enterovirus D68	*Streptococcus mutans (2)*
Herpes Simplex 1,2	*Streptococcus parasanguis*
Influenzae A (H1N1 and H3N2) virus	*Streptococcus sanguinis*
Influenzae B Virus	*Streptococcus aureus (6)*
ParaInfluenzae virus 1,2,3 (3)	*Streptococcus epidermidis (5)*
Respiratory Syncytial Virus A	*Streptococcus saprophyticus (3)*
Klebsiella oxytoca (2)	*Stenotrophomonas maltophilia*
Klebsiella pneumoniae (3)	*Streptococcus gr. A, B, C, F, L and G (16)*
Lactobacillus catenaforme	*Streptococcus mitis*
Lactobacillus rhamnosus	

All of the above bacterial isolates were negative when using ImmuView *S. pneumoniae* and *L. pneumophila* Urinary Antigen Test. The only potential cross-reactivity was 1 of 3 isolates of *E. cloacea* which was positive for *L. pneumophila*. This was confirmed on re-testing of that one isolate.

A total of 19 Urinary tract infection from patients were tested. Previously culture results had shown that eight (8) of them were infected with *Escherichia coli*, five (5) with *Staphylococcus, aureus,* five (5) with *Streptococcus agalactiae* gr. B and one (1) with *Candida albicans*. None showed any cross reactions with the ImmuView test.

Sensitivity (Limit of detection (LOD))

The limit of detection (LOD) for the ImmuView *S. pneumoniae* and *L. pneumophila* urinary antigen test is 62.5 pg/mL for purified *S. pneumoniae* CWPS antigen (native). For LPS specific for *L. pneumophila* SG1 (Philadelphia) the LOD is 25 ng/mL. Whole cell *S. pneumoniae* bacteria can be detected at an LOD at 10^5 CFU/mL and *L. pneumophila* SG1 (Philadelphia) has a LOD at 10^4 CFU/mL. Boiling or urine preservatives did not change these results.

Table 6

Stock solution	**LOD**
S. pneumoniae antigen	62.5 pg/mL
L. pneumophila SG 1 (Philadelphia) antigen	0.025 µg/mL
L. pneumophila SG 1 (Bellingham) antigen	0.5 µg/mL
S. pneumoniae (serotype 1)	10^5 CFU/mL
L. pneumophila SG1 (Philadelphia)	10^4 CFU/mL
L. pneumophila SG 1 (Bellingham)	10^5 CFU/mL

Strain Reactivity

Isolates from different *S. pneumoniae* serotypes were also positive tested with the ImmuView assay including serotype three (3), five (5), and thirty-seven (37). Different species of *L. pneumophila* were also found to be positive using the assay. Within serogroup one (1) these includes Philadelphia, Knoxville, OLDA/Oxford, Allentown/France, and Benidorm-Strain Lens. In additional studies have found other *Legionella* serogroups to be positive such as serogroup 3, 6, 8, 10 and 12.

Table 7

Streptococcus pneumoniae in urine				
Subgroup		Antigen Concentration (µg/mL)		Whole Organism Concentration (CFU/mL)
type 1		ND*		10^4
type 3		0.001		10^4
type 5		0.010		10^5
type 37		0.0001		ND*
Legionella pneumophila in urine				
Subgroup	Pontiac/Non-Pontiac	Species	Concentration (µg/mL)	Concentration (CFU/mL)
SG1	Pontiac	Knoxville	0.100	10^5
SG1	Pontiac	Allentown/France	0.005	ND*
SG1	Pontiac	Benidorm	ND	10^4
SG1	Pontiac	Philadelphia	0.010	10^4
SG1	Non-Pontiac	OLDA/Oxford	0.001	ND
SG1	Non-Pontiac	Camperdown	0.315	ND
SG1	Non-Pontiac	Heysham	1.250	ND

SG3			250	ND
SG6			250	ND
SG8			250	ND
SG10			250	ND
SG12			7.8	ND

**ND=Not done*

Interfering Substances

ImmuView *S. pneumoniae* and *L. pneumophila* Urinary Antigen Test were tested with forty-seven (47) interfering agents at different concentrations in urine samples.

Table 8

Agent	Concentration	Agent	Concentration
Acetaminophen	0.1mg/mL	Leucocytes	>250 cells/µL
Acetylsalicylic acid	0.1mg/mL	Miconazole	5%
Amantadine	0.03mg/mL	Mix (pH, whole blood, protein and glucose) (H)	
Amoxicillin	0.075mg/mL	Mix (pH, whole blood, protein and glucose) (M)	
Amphotericin B	0.22mg/mL	Mix (pH, whole blood, protein and glucose) (L)	
Antihistamine	0.22mg/mL	Mucin	0.086mg/mL
Ascorbic acid (C-Vitamin)	1mg/mL	Oseltamivir (Tamiflu)	0.03mg/mL
Augmentin (Amoxicillin Clavulanate)	0.22mg/mL	Oxalic acid	0.01%
Azithromycin	0.012mg/mL	pH (acidic)	4
Beet root	20%	pH (neutral)	7
Beet root	1.17%	pH (basic)	9
Beet root	0.01%	Plasma	90%
Bilirubin	0.2mg/mL	Plasma	50%
Bromhexin/cough drops/couch syrup	0.22mg/mL	Plasma	10%
Caffeine	15mg/mL	Prednisone	0.22mg/mL
Chlorophyll	0.11mg/mL	Protein (albumin) (H)	10mg/mL
Chlorophyll	0.04mg/mL	Protein (albumin) (M)	5mg/mL
Chlorophyll	0.01mg/mL	Protein (albumin) (L)	0.6mg/mL
Ciprofloxacin	0.22mg/mL	Pyridium	1mg/mL
Decongestant	0.22mg/mL	Rifampicin	0.09mg/mL
Corticosterone (Corticosteroids)	0.015mg/mL	Spinach	1%
Erythromycin	0.067mg/mL	Tobacco purified	0.4mg/mL
Glucose (H)	20mg/mL	Triglycerides	4mg/mL
Glucose (M)	10mg/mL	Urea	20mg/mL
Glucose (L)	3mg/mL	Vaginal contraceptive gel	5%
Hemoglobin	5mg/mL	Vancomycin	0.1mg/mL
Human albumin	35mg/mL	Water-based personal lubricant	5%
Human red blood cells 10% Washed pooled cells	10%	White blood cells	10%
Ibuprofen	0.1mg/mL	Whole blood	10%
Itraconazole	0.22mg/mL	Whole blood	15%

High concentration of plasma in urine may result in gray test lines. Additionally, basic (pH≥9) conditions in urine can give false positive *S. pneumoniae* lines. Water-based personal lubricant might result in false positive or gray *L. pneumophila* lines, however, this outcome seems dose-related.

Clinical sensitivity and specificity - CSF

The sensitivity of the *S. pneumoniae* test line was obtained by testing leftover CSF specimens from patients suspected of meningitis, as well as spiked CSF and negative CSF table 10 below.

Table 9

ImmuView	S.pn. Culture positive	S.pn. Culture negative
S.pn. Positive	13	7
S.pn. Negative	1	162
Total	14	169
sensitivity	92.9% (13/14)	95% CI (68.5%-98.7%)
specificity	96.0% (162/169)	95% CI (91.7%-98.0%)

U.S.A Laboratory testing

Of the samples tested at the two U.S. labs, 9 were known positive for *S. pneumoniae* meningitis. One-hundred-thirteen (113) were negative human CSF samples. These samples were blinded, and the testing of the ImmuView Test was performed by three operators on different days to prevent test bias.

European Laboratory testing

Of the samples tested within Europe, 5 were known to be positive for *S. pneumoniae*. Of the total samples, 56 were negative CSF samples. These samples were blinded and the testing with the ImmuView Test was performed by one operator on different
days to prevent test bias.

The sensitivity of ImmuView *L. pneumophila* test line was not validated in this study, *Legionella* do not usually cause meningitis.

Spiked CSF testing

Additional human CSF samples were spiked at the LOD with *S. pneumoniae* (N=50) and an additional unspiked negative CSF samples (N=10) were tested with the Immuview test and the comparator test. The sensitivity for the both the ImmuView test and the comparator test was 50/50 (100%) and the additional negative CSF samples used for blinding of the testing were negative 10/10 (100%) in both the ImmuView test and the comparator test.

Table 10

60 real human CSF samples 50 spiked with *S. pneumoniae*			
ImmuView	Comparator		
	S.pn. Positive	S.pn. Negative	Total
S.pn. Positive	50	0	50
S. pn. Negative	0	10	10
Positive percent agreement	100%	95% CI (92.9%-100%)	
Negative percent agreement	100%	95% CI (72.2%-100%)	

Analytical Studies - CSF

Specificity (Cross-Reactivity)

ImmuView *S. pneumoniae* and *L. pneumophila* Urinary Antigen Test were tested with a panel of 24 potential cross-reacting agents. No cross-reactions were detected for the *S. pneumoniae* or the *L. pneumophila* test lines.

Table 11

Organisms not affecting test performance in CSF	
E. coli (5)	*Neisseria meningitidis* Gr. B, D and W135 (3)
Haemophilus influenza type a-f and non-caps (7)	*Staphylococcus aureus*
Listeria monocytogenes	*Streptococcus* Gr A
Measles	*Streptococcus agalactiae* (GBS) sg Ia, Ib, II, III (4)
	Streptococcus mitis

Sensitivity (Limit of detection (LOD)) in CSF

ImmuView *S. pneumoniae* and *L. pneumophila* analytical sensitivity was determined by limit of detection. Two different operators performed the dilutions and the testing. The dilutions were made with whole cell bacteria spiked in human CSF.

Table 12

CSF	**LoD**
S. pneumoniae	10^3 CFU/mL

Interference agents

ImmuView *S. pneumoniae* and *L. pneumophila* Urinary Antigen Test were tested with forty-seven (47) interfering agents at different concentrations in artificial CSF either negative or spiked with either CWPS or *S. pneumoniae* 10^7 CFU/mL.

Table 13

Agent in CSF	**Concentration**	**Agent**	**Concentration**
Whole *S. pneumoniae* (Type 1)		**Negative Artificial CSF**	
Glucose (H)	1mg/mL	Glucose (H)	1mg/mL
Glucose (M)	0.5mg/mL	Glucose (M)	0.5mg/mL
Glucose (L)	0.1mg/mL	Glucose (L)	0.1mg/mL
Red blood cells (H)	15%	Red blood cells (H)	15%
Red blood cells(M)	10%	Red blood cells(M)	10%
Red blood cells (L)	5%	Red blood cells (L)	5%
Protein (H)	60mg/mL	Protein (H)	60mg/mL
Protein (M)	30mg/mL	Protein (M)	30mg/mL
Protein (L)	10mg/mL	Protein (L)	10mg/mL
White blood cells	$10.6x10^6$/mL	White blood cells	$10.6x10^6$/mL
White blood cells	$5.3x10^6$/mL	White blood cells	$5.3x10^6$/mL
White blood cells	$2.7x10^6$/mL	White blood cells	$2.7x10^6$/mL
White blood cells	$1.8x10^6$/mL	White blood cells	$1.8x10^6$/mL
White blood cells	$0.9x10^6$/mL	White blood cells	$0.9x10^6$/mL
		Bilirubin	
Antigen		Bilirubin	
Bilirubin	15%	Bilirubin	
Bilirubin	10%	Plasma	
Bilirubin	5%	Plasma	
Plasma	15%	Plasma	
Plasma	10%		
Plasma	5%		

Red blood cells may give false positive shadows on the *S. pneumoniae* line due to excessive red color. The other agents in the panel did not interfere with the test.

Reproducibility study

The ImmuView *S. pneumoniae* and *L. pneumophila* Urinary Antigen test demonstrated excellent overall reproducibility with 1,068 correct results out of 1,072 test results (99.6%), when tested with 10 members of real positive *S. pneumoniae* or *L. pneumophila* urine samples and negative urine samples; and artificial CSF positive spiked with *S. pneumoniae* isolates as well as negative artificial CSF samples. The ImmuView Positive Control and Negative Control were also tested as blinded/masked panel members. The testing was performed for 5 days with a different kit lot at each site, two in the U.S. and one in Europe.

Table 14

Description	Correct results	Agreement
S. pneumoniae, moderate positive urine	90/90 Positive	100.0%
S. pneumoniae, moderate positive CSF	89/89[2] Positive	100.0%
S. pneumoniae, low positive spiked in artificial CSF	89/90[3] Positive	98.9%
S. pneumoniae, low positive urine	90/90 Positive	100.0%
L. pneumophila, moderate positive urine 2A	90/90 Positive	100.0%
L. pneumophila, moderate positive urine 2B	88/89[4] Positive	98.9%
L. pneumophila, low positive urine 1A	89/89[5] Positive	100.0%
L. pneumophila, low positive urine 1B	89/90[6] Positive	98.9%
Negative pooled urine	90/90 Negative	100.0%
Negative artificial CSF	90/90 Negative	100.0%
ImmuView Pos Control	89/90[7] Positive	98.9%
ImmuView Neg Control	85/85[8] Negative	100.0%
Summary	**1068/1072 Correct**	**99.6%**

A total of 3 different lots were tested. Each site, using two operators (A and B) performed a total of 360 reproducibility tests and a grand total of 1,072 reproducibility results out of a total of 1,080 tests in the study using 6 operators. A total of 8 test results (0.7%) were determined to be invalid and were excluded and not re-tested. The panel members were blinded by changing of the panel member numbers and identity daily. The reading and interpretation of the reproducibility panels was performed visually. There were no statistical differences in reproducibility by lot, by site, by time or by operator.

1. The protocol was run five different days, each day each sample had a different code number.

2. Operator did not see a positive control band, so one sample was invalid as the package insert states that this is necessary before interpreting the result. The sample was not re-tested.

3. A visual *L. pneumophila* band was seen.

4. Operator interpreted band as *S. pneumoniae* positive instead of *L. pneumophila* positive. One sample was invalid due to dot (incomplete band) on the strip per the package insert and was not re-tested.

5. One sample was invalid due to an incomplete band in *S. pneumoniae* according to the pack insert.

6. No *L. pneumophila* band present.

7. Operator interpreted *S. pneumoniae* Band result as negative even though band was present.

8. Five samples excluded due to the presence of dots and incomplete bands. The samples were not re-tested.

References

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