SPECIAL 510(K): DEVICE MODIFICATION
OIR DECISION SUMMARY

510(k) Number: _K182157_

This 510(k) submission contains information/data on modifications made to the applicant's own class II device requiring 510(k). The following items are present and acceptable:

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1. The name and 510(k) number of the applicant's previously cleared device.

510(k) Number	Device Name	Clearance Date	Primary Reason for 510(k) Submission
K133474	BioSign® Flu A+B	12/10/2013	K133474 was the most recent regulatory action for this device, originally cleared as K083746 on 11/10/2010. K133474 was a special 510(k) submission for device modification to expand the Analytical Inclusivity section of the package insert to include reactivity information for two strains of the H5N1 subtype of influenza A virus, A/Vietnam/1194/2004 and A/Anhui/01/2005.

2. Applicant's statement that the **INDICATION/INTENDED USE** of the modified device as described in its labeling **HAS NOT CHANGED** along with the proposed instructions for use.

3. A description of the device **MODIFICATION(S)** in sufficient detail to demonstrate that the **FUNDAMENTAL SCIENTIFIC TECHNOLOGY** of the modified device **has not changed**.

   A. PBM conducted an additional clinical study during the 2017 to 2018 influenza season, testing nasophyngeal aspirate specimens sequencially obtained from a state public health laboratory, against an FDA-cleared RT-PCR assay (see Section 6 below). The results of this additional study demonstrate that the BioSign Flu A+B performance for testing nasophyngeal aspirate/wash specimens meet the performance criteria specified in 21 CFR 866.3328.

   B. The product package insert has been revised for the modified device, reflecting a re-organization of the Clinical Performance section as follows:

      1) Prospective Clinical Study from 2007 to 2009
         a) Nasophyngeal Aspirate Samples: Performance against Viral Culture
         b) Nasophyngeal/Nasal Swab Samples: Performance against Viral Culture
         c) Nasophyngeal/Nasal Swab Samples: Performance against an FDA-cleared RT-PCR Assay
      2) Prospective Clinical Study from 2014 to 2016
         a) Nasophyngeal/Nasal Swab Samples: Performance against an FDA-cleared RT-PCR Assay
      3) All Prospective Clinical Studies Combined (2007 to 2009 and 2014 to 2016)
         a) Nasophyngeal/Nasal Swab Samples: Performance against an FDA-cleared RT-PCR Assay
      4) Clinical Study from 2017 to 2018

a) Nasophyngeal Aspirate/Wash Samples: Performance against an FDA-cleared RT-PCR Assay

Table 1 below is a new performance table based on the re-analysis of the performance data generated from the 2007 to 2009 prospective clinical study, testing nasophyngeal (NP) swab and nasal swab specimens, against virus culture. This table is added to section 1b) of the Clinical Performance section of the revised product package insert as described above.

Table 1: Nasophyngeal/Nasal Swab Samples - Performance against Viral Culture (Prospective Clinical Study from 2007 to 2009)

	Viral Culture Results			
BioSign Flu A+ B	Flu A Positive	Flu A Negative	Total	Performance
Flu A Positive	59	131	190	Sensitivity: 90.8% 95% CI: 81.3-95.7%
Flu A Negative	6	413	419	Specificity: 75.9% 95% CI: 72.2-79.3%
Total	65	222	609	

	Viral Culture Results			
BioSign Flu A+ B	Flu B Positive	Flu B Negative	Total	Performance
Flu B Positive	47	55	102	Sensitivity: 85.5% 95% CI: 73.8-92.4%
Flu B Negative	8	499	507	Specificity: 90.1% 95% CI: 87.3-92.3%
Total	55	554	609	

Table 2 below is a new performance table based on a re-analysis of the performance data generated from the 2007 to 2009 prospective clinical study, testing nasophyngeal swab and nasal swab specimens, against an FDA-cleared RT-PCR assay. This re-analysis of the prospective performance data was conducted employing a statistical method to project results for the specimens with missing data from the FDA-cleared RT-PCR comparator assay in the 2007 to 2009 prospective clinical study. The statistical method employed in this data re-analysis is consistent with the principles outlined in the FDA guidance document entitled *Design Considerations for Pivotal Clinical Investigations for Medical Devices: Guidance for Industry, Clinical Investigators, Institutional Review Boards and Food and Drug Administration Staff.* This table is added to section 1c) of the Clinical Performance section of the revised product package insert as described above.

Table 2: Nasophyngeal/Nasal Swab Samples - Performance against an FDA-cleared RT-PCR Assay (Prospective Clinical Study from 2007 to 2009)

	RT-PCR Results			
BioSign Flu A+ B	Flu A Positive	Flu A Negative	Total	Performance
Flu A Positive	165	25	190	Sensitivity: 92.2% 95% CI: 87.3-95.3%
Flu A Negative	14	405	419	Specificity: 94.2% 95% CI: 91.6-96.0%
Total	179	430	609	

	RT-PCR Results			
BioSign Flu A+ B	Flu B Positive	Flu B Negative	Total	Performance
Flu B Positive	72	30	102	Sensitivity: 90.0% 95% CI: 81.5-94.8%
Flu B Negative	8	499	507	Specificity: 94.3% 95% CI: 92.0-96.0%
Total	80	529	609	

Table 3 below is a new performance table based on the analysis of a subset of the performance data generated from the 2014 to 2016 CLIA Waiver clinical study that represents all prospective performance data generated from the 2014 to 2016 CLIA Waiver clinical study testing nasophyngeal swab and nasal swab specimens. This table is added to section 2a) of the Clinical Performance section of the revised product package insert as described above.

Table 3: Nasophyngeal/Nasal Swab Samples - Performance against an FDA-cleared RT-PCR Assay (Prospective Clinical Study from 2014 to 2016)

	RT-PCR Results			
BioSign Flu A+ B	Flu A Positive	Flu A Negative	Total	Performance
Flu A Positive	101	2	103	Sensitivity: 90.2% 95% CI: 83.3-94.4%
Flu A Negative	11	193	204	Specificity: 99.0% 95% CI: 96.3-99.7%
Total	112	195	307	

	RT-PCR Results			
BioSign Flu A+ B	Flu B Positive	Flu B Negative	Total	Performance
Flu B Positive	27	3	30	Sensitivity: 81.8% 95% CI: 65.9-91.4%
Flu B Negative	6	271	277	Specificity: 98.9% 95% CI: 96.8-99.6%
Total	33	274	307	

Table 4 below is a new performance table based on the analysis of all the performance data generated from the 2007 to 2009 and the 2014 to 2016 prospective clinical studies testing nasophyngeal swab and nasal swab specimens. This table is added to section 3a) of the Clinical Performance section of the revised product package insert as described above.

Table 4: Nasophyngeal/Nasal Swab Samples - Performance against an FDA-cleared RT-PCR Assay (Prospective Clinical Study from 2007 to 2009 and Prospective Clinical Study from 2014 to 2016)

	RT-PCR Results			
BioSign Flu A+ B	Flu A Positive	Flu A Negative	Total	Performance
Flu A Positive	266	27	293	Sensitivity: 91.4% 95% CI: 87.6-94.1%
Flu A Negative	25	598	623	Specificity: 95.7% 95% CI: 93.8-97.0%
Total	291	625	916	

	RT-PCR Results			
BioSign Flu A+ B	Flu B Positive	Flu B Negative	Total	Performance
Flu B Positive	99	33	132	Sensitivity: 87.6% 95% CI: 80.3-92.5%
Flu B Negative	14	770	784	Specificity: 95.9% 95% CI: 94.3-97.1%
Total	113	803	916	

Table 5 below is a new performance table based on the analysis of performance data generated from a new 2017 to 2018 clinical study (see Section 6 below) testing nasophyngeal (NP) aspirate/wash specimens. This table is added to section 4a) of the Clinical Performance section of the revised product package insert as described above.

Table 5: Nasophyngeal Aspirate/Wash Samples - Performance against an FDA-cleared RT-PCR Assay (Clinical Study from 2017 to 2018)

	RT-PCR Results			
BioSign Flu A+ B	Flu A Positive	Flu A Negative	Total	Performance

	RT-PCR Results			
BioSign Flu A+ B	Flu B Positive	Flu B Negative	Total	Performance

Flu A Positive	126	0	126	Sensitivity: 85.1% 95% CI: 78.5-90.0%
Flu A Negative	22	78	100	Specificity: 100% 95% CI: 95.3-100%
Total	148	78	226	

Flu B Positive	36	1	37	Sensitivity: 85.7% 95% CI: 72.2-93.3%
Flu B Negative	6	183	189	Specificity: 99.5% 95% CI: 97.0-99.9%
Total	42	184	226	

4. **Comparison Information** (similarities and differences) to applicant's legally marketed predicate device.

Item	**Predicate Device**	**Modified Device**
Features	**BioSign® Flu A+B (K133474)**	**BioSign® Flu A+B (K182157)**
Intended Use	BioSign® Flu A+B is an *in vitro* rapid qualitative test that detects influenza type A and type B nucleoprotein antigens directly from nasal swab, nasopharyngeal swab, and nasopharyngeal aspirate/wash specimens obtained from patients with signs and symptoms of respiratory infection. It is intended to aid in the rapid differential diagnosis of influenza A and B viral infections. Negative test results are presumptive and it is recommended these results be confirmed by viral culture. Negative results do not preclude influenza virus infection and should not be used as the sole basis for treatment or other management decisions. The test is intended for professional and laboratory use. Performance characteristics for influenza were established during the 2007-2009 influenza seasons when influenza A viruses A/New Caledonia/20/99 (H1N1), A/Solomon Islands/3/2006 (H1N1), A/Brisbane/59/2007 (H1N1), A/California/07/2009 (H1N1), A/Wisconsin/67/2005 (H3N2), A/Brisbane/ 10/2007 (H3N2) and influenza B viruses B/Ohio/01/2005, B/Florida/4/2006, B/Brisbane/60/2008 were the predominant influenza viruses in circulation according to the Flu Activity & Surveillance report by CDC. Performance characteristics may vary against other emerging influenza viruses. If infection with a novel influenza virus is suspected based on current clinical and epidemiological screening criteria recommended by public health authorities, specimens should be collected with appropriate infection control precautions for novel virulent influenza viruses and sent to state or local health department for testing. Viral culture should not be attempted in these cases unless a BSL 3+ facility is available to receive and culture specimens.	BioSign® Flu A+B is an *in vitro* rapid qualitative test that detects influenza type A and type B nucleoprotein antigens directly from nasal swab, nasopharyngeal swab, and nasopharyngeal aspirate/wash specimens obtained from patients with signs and symptoms of respiratory infection. It is intended to aid in the rapid differential diagnosis of influenza A and B viral infections. Negative test results are presumptive and it is recommended these results be confirmed by viral culture or an FDA-cleared influenza A and B molecular assay. Negative results do not preclude influenza virus infection and should not be used as the sole basis for treatment or other management decisions. Performance characteristics for influenza were established during the 2007-2009 and the 2014-2016 influenza seasons when influenza A/H1N1, A/H1N1 pandemic, A/H3N2, influenza B/Victoria lineage, and B/Yamagata lineage were the predominant influenza viruses in circulation according to the Flu Activity & Surveillance report from the CDC. When other influenza viruses are emerging, performance characteristics may vary. If infection with a novel influenza virus is suspected based on current clinical and epidemiological screening criteria recommended by public health authorities, specimens should be collected with appropriate infection control precautions for novel virulent influenza viruses and sent to state or local health department for testing. Viral culture should not be attempted in these cases unless a BSL 3+ facility is available to receive and culture specimens.
Specimen Types	Nasopharyngeal swabs, nasal swabs, and nasopharyngeal aspirate/wash specimens, from patients with signs and symptoms of respiratory infection.	Same
Analitical Principle	Solid phase chromatographic immunoassay	Same

Item	Predicate Device	Modified Device
Features	**BioSign® Flu A+B (K133474)**	**BioSign® Flu A+B (K182157)**
Extraction	Incubated for 1 minute in the extraction reagent	Same
Result Read Time	10 minutes	Same
Test Line	Colloidal gold	Same
Internal Control Line	Reddish-purple line	Same
Control Samples (supplied as prepared swabs)	Positive Control Swab: Influenza A and B antigens (non-infective recombinant nucleoprotein) Negative Control Swab: Inactivated Group B *Streptococcus* antigen (non-infective)	Same
Product Package Insert	See K133474	Clinical Performance section of the product package insert is revised and re-organized.

5. A **Design Control Activities Summary** which includes:

   a) Identification of Risk Analysis method(s) used to assess the impact of the modification on the device and its components, and the results of the analysis.

   The risk assessment process was based on Princeton BioMeditech (PBM) internal Risk Management process (QA#11800), which meets the requirements of ISO14971:2012. According to the procedure, a failure mode and effect analysis (FMEA) has been used for analysis of the risk and the following items are analyzed:
   - The hazard
   - Failure Mode
   - Potential Effect of Failure
   - Potential Cause/Mechanism of Failure
   - Mitigating Factors (any existing control measure)
   - The probability of hazard severity, occurrence, and detectability

   b) Based on the Risk Analysis, an identification of the verification and/or validation activities required, including methods or tests used and acceptance criteria to be applied.

   Based on a resulting calculated risk index, risk control measures are identified, required verification and validation activities are determined, and verification of the effectiveness of risk control measures is determined.

   1) The inclusion of the additional performance tables for nasopharrygeal swab and nasal swab specimens against an FDA-cleared RT-PCR assay in the Clinical Performance section of the product package insert (PI) does not create any new product risks. There has been no change in the product formulation. The change is exclusively a labeling change. The current performance being observed by customers will not change as there is no change to the design or production process for this product. Therefore, because the addition of performance tables does not impact the risk associated with the device, the current risk assessment table will not change.

2) PBM conducted an additional clinical study during the 2017 to 2018 influenza season, testing nasophyngeal aspirate specimens sequencially obtained from a state public health laboratory, against an FDA-cleared RT-PCR assay (see Section 6 below). The results of this additional study demonstrate that the BioSign Flu A+B performance for testing nasophyngeal aspirate/wash specimens meet the performance criteria specified in 21 CFR 866.3328. The inclusion of an additional performance table for nasopharrygeal aspirate specimens against an FDA-cleared RT-PCR assay in the Clinical Performance section of the product package insert (PI) does not create any new product risks. There has been no change in the product formulation. The change is exclusively a labeling change. The current performance being observed by customers will not change as there is no change to the design or production process for this product. Therefore, because the addition of performance tables does not impact the risk associated with the device, the current risk assessment table will not change.

6. **Clinical Performance**

A supplementary clinical study was conducted to collect additional data for assessing BioSign Flu A+B performance compared against an FDA-cleared RT-PCR assay for nasopharyngeal aspirate/wash specimens, and to demonstrate that the BioSign Flu A+B performance for testing nasopharyngeal aspirate/wash specimens meets the performance criteria specified in 21 CFR 866.3328.

From October 2017 to March 2018, residual nasopharyngeal aspirate/wash samples were sequentially collected from the specimens that were received at a state public health laboratory for influenza confirmation testing. The state public health laboratory recorded the specimen collection date, gender, and age for each patient from whom the specimen was collected on a log sheet as each specimen was received at the laboratory for influenza confirmation testing. The samples were blinded and numbered before they were frozen at -70º C and shipped to PBM on dry ice.

Samples received at PBM were thawed and tested using the BioSign Flu A+B test[1] according to the standard procedure in the package insert. The remaining sample was frozen at -70º C and shipped frozen on dry ice to a reference laboratory for RT-PCR testing using an FDA-cleared influenza RT-PCR assay[2].

The total number of samples tested was 226, of which 147 samples were Flu A positive, 41 were flu B positive, one sample was both Flu A and Flu B positive, and 37 samples were both Flu A and Flu B negative by FDA-cleared influenza RT-PCR assay. Fifteen (15) percent of the total number of samples were from patients aged 5 and younger, 9% were from patients 6-21 years

[1] An internal analytical validation study conducted at PBM demonstrated that freeze/thaw of NP aspirate/wash specimens neither favorably nor adversely impact the performance of the BioSign Flu A+B.

[2] An internal analytical validation study conducted at the reference lablratory demonstrated that the limit of detection of the FDA-cleared influenza RT-PCR assay testing NP aspirate/wash specimens is equivalent to that of testing NP swab collected in VTM specimens. In addition, an internal analytical validation study conducted at the reference lablratory also demonstrated that the performance of the FDA-cleared influenza RT-PCR assay testing NP aspirate/wash specimens was not adversely impacted after three freeze/thaw cycles of the specimens.

old, and the remainder were from patients older than 21. Forty-four (44) percent of the total number of patients were male and 54% were female. For five of the samples the gender was not reported. Out of the 226 samples tested, there were no invalid BioSign Flu A+B test results.

The testing results compared against the FDA-cleared influenza RT-PCR assay are presented in Table 6 below.

Table 6: Nasophyngeal Aspirate/Wash Samples - Performance against an FDA-cleared RT-PCR Assay (Clinical Study from 2017 to 2018)

	RT-PCR Results			
BioSign Flu A+ B	Flu A Positive	Flu A Negative	Total	Performance
Flu A Positive	126	0	126	Sensitivity: 85.1% 95% CI: 78.5-90.0%
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	RT-PCR Results			
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7. **Conclusion**

The labeling for this modified subject device has been reviewed to verify that the indication/intended use for the device is unaffected by the modifications. In addition, the applicant's description of the particular modification(s) and the additional clinical study performance data generated from testing nasopharygeal aspirate/wash specimens demonstrate that the fundamental scientific technology has not changed. The applicant has provided the design control information as specified in The New 510(k) Paradigm and on this basis, I recommend the device be determined substantially equivalent to the predicate device.