

## **SPECIAL 510(k): Device Modification OIR Decision Summary**

**To:** Alere Scarborough, Inc.

**RE:** K163266

This 510(k) submission contains information/data on modifications made to the SUBMITTER'S own Class II, Class III or Class I devices requiring 510(k). The following items are present and acceptable (delete/add items as necessary):

1. The name and 510(k) number of the SUBMITTER'S previously cleared device:

Alere i Influenza A & B

510(k) number: K151464

2. Submitter's statement that the **INDICATION/INTENDED USE** of the modified device as described in its labeling **HAS NOT CHANGED** along with the proposed labeling which includes instructions for use, package labeling, and, if available, advertisements or promotional materials (labeling changes are permitted as long as they do not affect the intended use).

3. Description of the device **MODIFICATION(S)**:

An additional molecular beacon has been added to the assay to address an identified mismatch with certain Flu B strains and the sugar excipient was modified to enable more efficient lyophilization and to further streamline the manufacturing process. The Alere i Influenza A & B assay package insert has been updated to include the additional analytical reactivity information.

4. The **FUNDAMENTAL SCIENTIFIC TECHNOLOGY** of the modified device **has not changed**.

5. **Comparison Information**

### Similarities

|              | <b>Modified Device</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | <b>Predicate Device</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|--------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Features     | Alere i Influenza A & B assay<br>(K163266)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Alere i Influenza A & B assay<br>(K151464)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Intended Use | The Alere™ i Influenza A & B assay performed on the Alere™ i Instrument is a rapid molecular <i>in vitro</i> diagnostic test utilizing an isothermal nucleic acid amplification technology for the qualitative detection and discrimination of influenza A and B viral RNA in direct nasal swabs and nasal or nasopharyngeal swabs eluted in viral transport media from patients with signs and symptoms of respiratory infection. It is intended for use as an aid in the differential diagnosis of influenza A and B viral infections in | The Alere™ i Influenza A & B assay performed on the Alere™ i Instrument is a rapid molecular <i>in vitro</i> diagnostic test utilizing an isothermal nucleic acid amplification technology for the qualitative detection and discrimination of influenza A and B viral RNA in direct nasal swabs and nasal or nasopharyngeal swabs eluted in viral transport media from patients with signs and symptoms of respiratory infection. It is intended for use as an aid in the differential diagnosis of influenza A and B viral infections in |

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|------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                        | <p>humans in conjunction with clinical and epidemiological risk factors. The assay is not intended to detect the presence of influenza C virus. Negative results do not preclude influenza virus infection and should not be used as the sole basis for diagnosis, treatment or other patient management decisions.</p> <p>Performance characteristics for influenza A were established during the 2012-2013 and the 2014-2015 influenza seasons when influenza A/H3 and A/H1N1 pandemic were the predominant influenza A viruses in circulation. When other influenza A viruses are emerging, performance characteristics may vary.</p> <p>If infection with a novel influenza A 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.</p> | <p>humans in conjunction with clinical and epidemiological risk factors. The assay is not intended to detect the presence of influenza C virus. Negative results do not preclude influenza virus infection and should not be used as the sole basis for diagnosis, treatment or other patient management decisions.</p> <p>Performance characteristics for influenza A were established during the 2012-2013 and the 2014-2015 influenza seasons when influenza A/H3 and A/H1N1 pandemic were the predominant influenza A viruses in circulation. When other influenza A viruses are emerging, performance characteristics may vary.</p> <p>If infection with a novel influenza A 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.</p> |
| Sample Type            | Same as predicate device                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Direct Nasal swab;<br>Nasal/Nasopharyngeal swab eluted in transport media                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Analytical Principle   | Same as predicate device                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Isothermal nucleic acid amplification                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Influenza A target     | Same as predicate device                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | PB2 gene segment RNA                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Influenza B target     | Same as predicate device                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | PA gene segment RNA                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Detection Method       | Same as predicate device                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Different reporter dyes for each target                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Internal Control       | Same as predicate device                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Yes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Results Interpretation | Same as predicate device                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Automated                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Assay Result           | Same as predicate device                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Qualitative                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Time to Result         | Same as predicate device                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | < 15 minutes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |

Differences

The package insert has been updated to include detection of the B/Wisconsin/1/2010, B/Malaysia/2506/2004, and B/Bangladesh/3333/2007 viruses at the following limits of detection:

## Limit of Detection – Natural Nasal Swab Matrix (Direct Swab Testing):

| Influenza Strain       | Lineage  | Test concentration in TCID <sub>50</sub> per mL | Test concentration in genome equivalents per mL |
|------------------------|----------|-------------------------------------------------|-------------------------------------------------|
| B/Wisconsin/1/2010     | Yamagata | $1.67 \times 10^3$                              | $3.39 \times 10^4$                              |
| B/Malaysia/2506/2004   | Victoria | $1.30 \times 10^3$                              | $2.35 \times 10^4$                              |
| B/Bangladesh/3333/2007 | Yamagata | $2.96 \times 10^2$                              | $2.61 \times 10^4$                              |

## Limit of Detection – Natural Nasal Swab Matrix (Swab Eluted in VTM Testing):

| Influenza Strain       | Lineage  | Test concentration in TCID <sub>50</sub> per mL | Test concentration in genome equivalents per mL |
|------------------------|----------|-------------------------------------------------|-------------------------------------------------|
| B/Wisconsin/1/2010     | Yamagata | $3.34 \times 10^4$                              | $6.57 \times 10^5$                              |
| B/Malaysia/2506/2004   | Victoria | $3.86 \times 10^4$                              | $7.06 \times 10^5$                              |
| B/Bangladesh/3333/2007 | Yamagata | $2.37 \times 10^4$                              | $2.31 \times 10^6$                              |

The package insert has been updated to include analytical reactivity results of nine influenza B viruses tested using the modified Alere i Influenza A & B Test. A summary of the reactivity testing results is shown in the table below:

| Influenza Strain       | Lineage  | Test concentration in TCID <sub>50</sub> per mL | Test concentration in genome equivalents per mL |
|------------------------|----------|-------------------------------------------------|-------------------------------------------------|
| B/Lee/40               | Victoria | $2.50 \times 10^2$                              | $4.85 \times 10^2$                              |
| B/Victoria/504/2000    | Victoria | $2.96 \times 10^2$                              | $1.09 \times 10^2$                              |
| B/Nevada/03/2011       | Victoria | $3.28 \times 10^2$                              | $1.07 \times 10^2$                              |
| B/Montana/05/2012      | Victoria | $5.45 \times 10^1$                              | $9.16 \times 10^1$                              |
| B/Brisbane/60/2008     | Victoria | $2.37 \times 10^2$                              | $5.76 \times 10^1$                              |
| B/Maryland/1/59        | Yamagata | $3.41 \times 10^3$                              | $8.88 \times 10^2$                              |
| B/Russia/69            | Yamagata | $1.88 \times 10^4$                              | $1.29 \times 10^5$                              |
| B/Massachusetts/2/2012 | Yamagata | $6.81 \times 10^3$                              | $3.29 \times 10^3$                              |
| B/Texas/06/2011        | Yamagata | $1.81 \times 10^2$                              | $3.79 \times 10^1$                              |

Minor grammatical changes were made within the package insert, but those changes do not affect the Intended Use.

**6. Design Control Activities Summary:**

A risk assessment of device modification was conducted and documented according to Alere Scarborough, Inc. Quality System requirements. The modification made to the assay does not affect the assay procedure and this change was not expected to impact the performance of the test or its safety and effectiveness. To confirm assay performance was not negatively impacted, Alere Scarborough Inc. performed the following validation studies:

- A. Limit of Detection (Direct Swab Assay Procedure)
- B. Limit of Detection (VTM Assay Procedure)
- C. Limit of Detection (Equivalency Study)
- D. Analytical Reactivity (Inclusivity)
- E. Analytical Reactivity (Comparison Study)

- F. Clinical Specimen Testing  
G. Shelf-Life (Stability)

Summary results of the Limit of Detection individual assay procedure testing and the Analytical Reactivity (Inclusivity) testing can be found in Section 5, above. A summary of the remaining validation studies can be found below:

#### Limit of Detection (Equivalency Study)

The purpose of this study was to demonstrate the modified Alere i Influenza A & B assay is capable of equivalent or better limit of detection compared to the current assay. Alere tested concentrations above and below the analytical LoD, as well as the determined LoD.

| Influenza Strain              | LoD Level | Concentration<br>TCID <sub>50</sub> /mL | Modified Assay  | Current Assay   |
|-------------------------------|-----------|-----------------------------------------|-----------------|-----------------|
|                               |           |                                         | Number Detected | Number Detected |
| A/Puerto Rico/8/34<br>(H1N1)  | 2x LoD    | $1.48 \times 10^5$                      | 20/20           | 20/20           |
|                               | LoD       | $7.39 \times 10^4$                      | 18/20           | 13/20           |
|                               | 0.5x LoD  | $3.70 \times 10^4$                      | 13/20           | 10/20           |
| A/Perth/16/2009<br>(H3N2)     | 2x LoD    | $8.44 \times 10^2$                      | 20/20           | 20/20           |
|                               | LoD       | $4.22 \times 10^2$                      | 19/20           | 18/20           |
|                               | 0.5x LoD  | $2.11 \times 10^2$                      | 18/20           | 9/20            |
| A/California/7/2009<br>(H1N1) | 2x LoD    | $1.80 \times 10^4$                      | 20/20           | 19/20           |
|                               | LoD       | $8.99 \times 10^3$                      | 19/20           | 8/20            |
|                               | 0.5x LoD  | $4.50 \times 10^3$                      | 13/20           | 4/20            |
| B/Malaysia/2506/2004          | 2x LoD    | $2.60 \times 10^3$                      | 20/20           | 20/20           |
|                               | LoD       | $1.30 \times 10^3$                      | 18/20           | 18/20           |
|                               | 0.5x LoD  | $6.49 \times 10^2$                      | 13/20           | 11/20           |
| B/Bangladesh/3333/2007        | 2x LoD    | $5.93 \times 10^2$                      | 20/20           | 20/20           |
|                               | LoD       | $2.96 \times 10^2$                      | 18/20           | 15/20           |
|                               | 0.5x LoD  | $1.48 \times 10^2$                      | 14/20           | 9/20            |
| B/Wisconsin/1/2010            | 2x LoD    | $3.34 \times 10^3$                      | 20/20           | 1/20            |
|                               | LoD       | $1.67 \times 10^3$                      | 20/20           | 0/20            |
|                               | 0.5x LoD  | $8.35 \times 10^2$                      | 18/20           | 0/19*           |

\* One sample generated an invalid result, testing was not repeated.

#### Analytical Reactivity (Comparison Study)

The purpose of this study was to demonstrate the modified Alere i Influenza A & B assay has equivalent or better analytical reactivity compared to the current assay. Initial virus concentrations were prepared until one device did not provide 3 out of 3 positive results. If testing resulted in one negative result on both devices, the devices were tested again with a 2-fold more concentrated preparation. Two-fold more concentrated virus preparations were tested until one device provided 3 out of 3 positive results during the comparison testing. Acceptance criterion was set as: 'the modified Alere i Influenza A & B assay must perform equivalent or better than the unmodified assay. The assay procedure used was the direct swab method.

| Strain                 | Concentration<br>TCID <sub>50</sub> /mL | Current Assay<br>Results | Modified Assay<br>Results |
|------------------------|-----------------------------------------|--------------------------|---------------------------|
| B/Lee/40               | $2.50 \times 10^2$                      | + / - / -                | + / + / +                 |
| B/Russia/69            | $3.76 \times 10^4$                      | + / + / -                | + / + / +                 |
|                        | $1.88 \times 10^4$                      | + / - / -                | + / + / -                 |
| B/Victoria/504/2000    | $1.18 \times 10^3$                      | + / - / -                | + / + / +                 |
|                        | $5.92 \times 10^2$                      | + / + / -                | + / + / -                 |
|                        | $2.96 \times 10^2$                      | + / - / -                | + / + / -                 |
| B/Maryland/1/59        | $3.41 \times 10^3$                      | + / - / -                | + / + / +                 |
| B/Brisbane/60/2008     | $9.48 \times 10^2$                      | + / + / -                | + / + / +                 |
|                        | $4.74 \times 10^2$                      | + / + / -                | + / + / -                 |
|                        | $2.37 \times 10^2$                      | + / - / -                | + / - / -                 |
| B/Massachusetts/2/2012 | $6.81 \times 10^3$                      | + / + / -                | + / + / +                 |
| B/Nevada/03/2011       | $3.28 \times 10^2$                      | + / + / -                | + / + / +                 |
| B/Montana/05/2012      | $1.09 \times 10^2$                      | + / + / -                | + / + / +                 |
|                        | $5.45 \times 10^1$                      | - / - / -                | + / - / -                 |
| B/Texas/06/2011        | $3.62 \times 10^2$                      | - / - / -                | + / + / +                 |
|                        | $1.81 \times 10^2$                      | + / - / -                | - / - / -                 |

The modified Alere i Influenza A & B Assay demonstrated superior analytical sensitivity in the detection of Influenza B compared to the current Alere i Influenza A & B Assay.

#### Clinical Sample Evaluation (Comparison Study)

The purpose of this study was to evaluate the clinical performance of the modified Alere i Influenza A & B test when testing retrospective clinical viral transport media samples, with performance compared to the current Alere i Influenza A & B assay when testing the same clinical samples. On each day of testing, a positive and a negative control swab were tested on both the current and modified Alere Influenza A & B tests. Each clinical sample was tested n=1 on both the current and modified Alere i Influenza A & B test according to the VTM assay procedure. Retrospective samples tested in this study are of a known influenza status based on PCR. For samples tested in this study, the sensitivity and specificity of the modified test must be equivalent to or higher than the current test. Results of the comparison testing are shown in the table below.

|                   | Current Assay | Modified Assay |
|-------------------|---------------|----------------|
| Flu A Sensitivity | 88.9% (24/27) | 88.9% (24/27)  |
| Flu A Specificity | 95.9% (47/49) | 100% (51/51)   |
|                   |               |                |
| Flu B Sensitivity | 95.9% (47/49) | 100% (51/51)   |
| Flu B Specificity | 98.7% (75/76) | 100% (76/76)   |

The invalid rate for the current Alere i Influenza A & B assay was 2.3% (3/128); the invalid rate for the modified Alere i Influenza A & B assay was 0.8% (1/128). The modified Alere i Influenza A & B assay has demonstrated equivalent or superior clinical performance compared to the current Alere i Influenza A & B assay.

### Shelf Life

Test Bases containing the modified reagents were stored at the appropriate temperature for up to four months. Following storage, QC samples and controls were tested according to the package insert. There was one invalid result (out of 106 tested) observed with the Flu B QC specimen group which was attributed to operator error. One false positive result (out of 51 tested) was observed in the presumed negative nasal swab group. All other samples provided the expected results. The results are consistent with the current Alere i Influenza A & B test and the modified test is expected to launch with at least a four month expiration. Alere intends to expand this expiration dating as is supported through ongoing shelf life validation testing.

A "Declaration of Conformity" statement was submitted for the manufacturing facility and validation activities and signed by the Regulatory Affairs manager and the Quality Assurance manager. The statements indicate that:

1. The manufacturing facility is in conformance with design control procedure requirements as specified in 21 CFR 820.30 and the records are available for review.
2. The validation activities, as required by the risk analysis, for the modification were performed by the designated individuals and the results demonstrated that the predetermined acceptance criteria were met.

In conclusion, based on the results of the analytical reactivity testing the modified labeling is truthful and accurate. The changes do not affect the performance of the test and it is therefore substantially equivalent to the current cleared test.

### **7. Truthful and Accurate Statement, a 510(k) Summary or Statement and the Indications for Use Enclosure.**

The labeling for this modified subject device has been reviewed to verify that the indication/intended use for the device is unaffected by the modification. In addition, the submitter's description of the particular modification(s) and the comparative information between the modified and unmodified devices demonstrate that the fundamental scientific technology has not changed. The submitter 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 previously cleared device.