SPECIAL 510(k): Device Modification
Review Memorandum

To: Hologic, Inc. (Gen-Probe Prodesse, Inc.) **RE:** K132237

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

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

   Prodesse® ProFAST™+ Assay
   510(k) number: K101855

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 and package labeling.

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

   The 510k submission contained modifications to the Internal Control and Positive Control as well as expanded Reactivity table to include one additional strain of Influenza A virus, Influenza A/Indiana/10/2011 (H3N2v). The modifications are summarized as follows:

   a. Outsourcing of the manufacturing of the Internal Control and subsequent minor changes to 5' and 3' ends of the internal control sequence.

      The current Internal Control (RIC) in ProFAST+ Assay contains a RNA *in vitro* transcript (IVT). The new Universal Internal Control (UIC-A) will contain a RNA *in vitro* transcript (IVT) and a DNA plasmid to allow users to perform one nucleic acid extraction and test with any combination of the Pro+ Series Assays including ProFlu+, ProhMPV+, ProParaflu+, ProFAST+, and ProAdeno+. Due to the different vector being used in the Universal Internal Control (UIC-A), minor changes were made to the 5' and 3' ends of the UIC-A sequence.

      The concentration of the RNA IVT in the Universal Internal Control (UIC-A) is the same as in the current Internal RNA Control (RIC). Handling of Universal Internal Control is identical to that of the current Internal RNA Control (RIC) included in the ProFAST+ Assay.

   b. The handling of the Positive Control for the ProFAST+ Assay will be changed to eliminate the customer dilution that occurs immediately prior to RT-PCR setup, effectively raising the testing concentration one log.

   c. Revise the reactivity table to include one additional strain of Influenza A, Influenza A/Indiana/10/2011 (H3N2v).
      The Influenza A/H3N2v can be detected at 10^3 $TCID_{50}$/mL.

4. **Comparison Information** (similarities and differences) to applicant's legally marketed predicate device including, labeling, intended use, and physical characteristics.

Similarities		
Element	**Modified Prodesse ProFAST+ Assay**	**Current Prodesse ProFst+ Assay (K101855)**
Organisms Detected	Same	Influenza A/H1, Influenza A/H3, Influenza A/2009 H1N1
Analyte	Same	RNA
Technological Principles	Same	Multiplex nucleic acid amplification
Specimen Types	Same	Nasopharyngeal Swab
User Complexity	Same	High
Sample Preparation Method	Same	Up front sample processing is required to extract nucleic acid.
Instrumentation	Same	bioMérieux NucliSENS easyMAG or Roche MagNA Pure and Cepheid SmartCycler II Instrument
Time to result	Same	Approximately 4 hours
Controls	Same	Internal control in each sample. External control processed with each batch of samples. (see below for differences)

Differences			
Element		**Modified ProFAST+ Assay**	**Current Prodesse ProFAST+ Assay**
Controls	Internal	• Universal Internal Control - Contains DNA plasmid in addition to RNA IVT • Control Stocks outsourced - Change in manufacturer leading to change in control vectors and minor sequence changes at the 5' and 3' ends of RNA IVT	• Internal RNA Control - Contains RNA IVT • Control stocks manufactured in house
	Positive	• PC does not require dilution; - PC is provided as "at use concentration"	• End user must dilute PC 1:10 prior to use for RT-PCR
Reactivity*	Influenza A/ Indiana/10/2011 (H3N2v)	• 10^3 $TCID_{50}$/mL	• none

*Although this test has been shown to detect influenza A/Indiana/10/2011 (H3N2v) cultured from positive human respiratory specimens, the performance characteristics of this device with clinical specimens that are positive for H3N2v influenza viruses have not been established.

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

   a. Identification of Risk Analysis method used to assess the impact of the modification on the device and its components, and the results of the analysis;
   Failure Mode and Effects Analysis (FMEA) was performed to determine whether the current design changes create new risks or failure modes or affect the risk priority number (RPN) value. No additional risk or change in RPN value was identified in the Risk Analysis.

b. To demonstrate that the modifications in Internal Control do not change the assay performance, Analytical Studies and a Comparison Study were conducted.

- Analytical Performances:

  - Analytical Sensitivity Confirmation

    The LoD, which was established in K101855, was confirmed for Influenza A/H1, Influenza A/H3, and Influenza A/2009 H1N1 when tested with the UIC-A side by side with the current RIC. The confirmed LoDs are as follows:

    Influenza A/H1 $5X\ 10^{-1}\ TCID_{50}/mL$

    Influenza A/H3 $5X\ 10^{-1}\ TCID_{50}/mL$

    Influenza A/2009 H1N1 $1X\ 10^{2}\ TCID_{50}/mL$

  - IC Interference Study

    The IC Interference Study demonstrated that the new control, UIC-A, did not inhibit the detection of target organisms at levels close to LoD.

  - Sample Stability Study

    The study demonstrated that the stability of the samples would not be affected by a change in the internal control.

  - Extractor Equivalency Studies

    The equivalency of nucleic acid extraction methods between the bioMérieux NucliSENS easyMAG automated extractor and Roche MagNA Pure LC extractor were evaluated by spiking the cultured and tittered strain of Influenza A into a negative nasopharyngeal swab (NPS) matrix pool at the confirmed LoD concentration. The study demonstrated equivalency between the two extraction methods.

- Comparison Study:

The comparison study was conducted for all Pro+ Series Assays including ProFlu+, ProhMPV+, ProParaflu+, ProFAST+, and ProAdeno+ using 366 positive samples and 66 negative samples. Among the 366 positive samples, 330 were retrospective pre-selected archived NPS specimens with 30 positive samples per target (11 targets total) and 36 were contrived samples, generated by spiking individual negative retrospective NPS samples with whole organism (Influenza A/Seasonal H1 or Parainfluenza 2). Each sample was split into 3 aliquots; one aliquot was tested using the current Internal RNA Control (RIC), one aliquot was tested using the Universal Internal Control (UIC-A), and one aliquot was tested using the current Universal Internal Control (UIA-P) for ProAdeno+ Assay. All samples were then split into 72 panels with 6 samples per panel, extracted and tested by four different operators. Half of the panel samples were extracted using the bioMérieux NucliSENS easyMAG method and the other half using the Roche MagNA Pure LC method. Of the 432 samples utilized in the study, 23 samples were removed from analysis due to the invalid controls or incomplete test results. The results for ProFAST+ Assay are summarized in the following tables:

ProFAST+ Assay IA/Seasonal H1 Results					
		Samples with RIC			
		Positive	Negative	Total	Comments
Samples with UIC-A	Positive	30	0	30	Percent Positive Agreement 100% (88.7% - 100%) 95% CI
	Negative	0	379	379	Percent Negative Agreement 100% (99.0% - 100%) 95% CI
Total		30	379	409	

ProFAST+ Assay IA/Seasonal H3 Results					
		Samples with RIC			
Samples with UIC-A		Positive	Negative	Total	Comments
	Positive	37	2*	39	Percent Positive Agreement 100% (90.6% - 100.0%) 95% CI
	Negative	0	370	370	Percent Negative Agreement 99.5% (98.1% - 99.9%) 95% CI
Total		37	372	409	

*Samples Influenza A/H1 positive with original source laboratory method (Luminex RVP)

ProFAST+ Assay IA/2009 H1N1 Results					
		Samples with RIC		Total	
Samples with UIC-A		Positive	Negative	Total	Comments
	Positive	48	0	48	Percent Positive Agreement 100% (92.6% - 100%) 95% CI
	Negative	0	361	361	Percent Negative Agreement 100% (99.0% - 100.0%) 95% CI
Total		48	361	409	

The results of analytical studies and the clinical study confirmed the original performance claims of the ProFAST+ Assay and demonstrated that assay performance was not affected by the incorporation of the modified Universal Internal Control (UIC-A). The ProFAST+ Assay package insert has been updated to reflect the changes in the controls

c. To evaluate whether eliminating customer dilution prior to RT-PCR setup will affect the effectiveness of the Positive Control at detecting any errors occurred in the target channels, several defective mixtures that either lacked the *Taq* polymerase or MMLV, or did not include sufficient concentration of reverse primers, or contained a PCR inhibitor were tested with Positive Control at supplied concentration without customer dilution. The study demonstrated that the Positive Control used at the supplied concentration could effectively detect any global errors in the target channels. The ProFAST+ Assay package insert has been updated to reflect the changes in the Positive Control.

d. To assess the reactivity of the ProFAST+ Assay with influenza A (IA) H3N2v virus, a cultured and tittered strain of H3N2v, obtained from CDC, was diluted in series to near the assay cutoff. The study results showed that the ProFAST+ Assay can detect Influenza A/H3N2v at 10^3 $TCID_{50}$/mL.

Although this test has been shown to detect influenza A/Indiana/10/2011 (H3N2v) virus cultured from positive human respiratory specimens, the performance characteristics of this device with clinical specimens that are positive for H3N2v influenza virus have not been established.

The ProFAST+ Assay package insert has been updated to include the revised reactivity table.

e. A declaration of conformity with design controls was submitted for the manufacturing facility which includes:
   i) A statement signed by the Senior Director of R & D, Gen-Probe Prodesse, Inc., was submitted confirming that, as required by the risk analysis, all verification and validation activities were performed by the designated individual(s) and the results demonstrated that the predetermined acceptance criteria were met, and
   ii) A "Declaration of Conformity" statement signed by the Associate Director of Quality and Regulatory, Gen-Probe Prodesse, Inc., was submitted stating that 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.

6. A **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 (or their preamendment) device.