SPECIAL 510(k): Device Modification
Review Memorandum

To: Hologic, Inc. (Gen-Probe Prodesse, Inc.) **RE:** K132159

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® ProAdeno™+ Assay
   510(k) number: K102952

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 Controls. The modifications are summarized as follows:

   a. Outsourcing of the manufacturing of the Internal Control resulted in minor changes made to the current Internal Control (UIC-P);
      - Modification made to the current Universal Internal Control (UIC-P);
        The current Universal Internal Control (UIC-P) in ProAdeno+ Assay contains a dsDNA PCR product. The modified 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+.
      - Minor changes made to the UIC-A sequence;
        Due to the different vector being used in the modified Universal Internal Control (UIC-A), minor changes were made to the 5' and 3' ends of the UIC-A sequence.
      - The concentration of the dsDNA control is increased from 10^4 copies/µL to 5 x 10^4 copies/µL. Handling of the modified Universal Internal Control is identical to that of the current Universal Internal Control (UIC-P) included in the ProAdeno+ Assay.

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

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

	Similarities	
Element	**Modified Prodesse ProFlu+ Assay**	**Current Prodesse ProFlu+ Assay (K110968)**
Organisms Detected	Same	Human adenovirus
Analyte	Same	DNA
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 3 hours
Controls	Same	Internal control in each sample. External control processed with each batch of samples. (see below for differences)

Differences			
Element		**Modified ProFlu+ Assay**	**Current Prodesse ProFlu+ Assay**
Controls	Internal	• Control Stocks outsourced - Change in manufacturer leading to change in control vectors and minor sequence change at the 5' and 3' ends of RNA IVT and change from PCR product to plasmid. - The concentration of the DNA control was increased from 10^4 copies/µL to 5 x 10^4 copies/µL.	• 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

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

a. Identification of Risk Analysis method used to assess the impact of the modification on the device.
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 Universal Internal Control (UIC-A) do not change the assay performance, Analytical Studies and a Comparison Study were conducted.
- <u>Analytical Performances:</u>
  - Analytical Sensitivity Confirmation
    LoD, which was established in K102952 in 2010, was confirmed for Adenovirus using three strains of adenovirus tested side by side with the modified Universal Internal Control (UIC-A) and with the current Universal Internal Control (UIC-P). The confirmed LoDs are as follows:
    HAdV-3 1X 10^0 $TCID_{50}$/mL

HAdV-4 1X 10^{-1} $TCID_{50}$/mL
HAdV-19 1X 10^{0} $TCID_{50}$/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 the 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 HAdV-3 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 new 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. The samples spiked with the current UIC-P and samples spiked with the modified UIC-A were also compared to the original source laboratory results when the specimens were tested with Luminex RVP. The study demonstrated that the modified UIC-A did not change the assay performance.

The ProAdeno+ Assay package insert has been updated to reflect the changes in the internal control.

c. To assess the stability of the modified Universal Internal Control (UIC-A), an accelerated stability study for the UIC-A stored at -70°C and a freeze-thaw stability study were conducted with one lot of each assay component. The studies demonstrated that the modified UIC-A can be stored at the same condition (≤ -70°C for 18 months with up to 2 freeze thaw cycles) as the current Universal Internal Control (UIC-P).

d. To evaluate whether eliminating customer dilution prior to PCR setup will affect the effectiveness of the Positive Control at detecting any errors occurred in the FAM (HAdV) Channel, several defective mixtures that either do not have the *Taq* polymerase, or do not have enough reverse primers, or contain a PCR inhibitor, were tested with Positive Control at supplied concentration without customer dilution. The study demonstrated that the Adenovirus DNA Control used at the supplied concentration can effectively detect any global errors in the FAM (HAdV) Channel. The Pro Adeno+ Assay package insert has been updated to reflect the changes in the Positive Control.

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.