cobas® HIV-1/HIV-2 Qualitative
and
cobas® HIV-1

510(k) Summary – BK251286

This summary of 510(k) safety and effectiveness information is being submitted in accordance with the requirements of 21 CFR 807.92.

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Proprietary Name	**cobas**® HIV-1/HIV-2 Qualitative nucleic acid test for use on the **cobas**® 5800/6800/8800 systems; **cobas**® HIV-1 Quantitative nucleic acid test for use on the **cobas**® 5800/6800/8800 Systems
Common Name	**cobas**® HIV-1/HIV-2 Qualitative; **cobas**® HIV-1
Classification Name	Human immunodeficiency virus (HIV) nucleic acid (NAT) diagnostic and/or supplemental test; Human immunodeficiency virus (HIV) viral load monitoring test
Product Codes	QST; QUM
Predicate Devices	**cobas**® HIV-1/HIV-2 Qualitative nucleic acid test for use on the **cobas**® 5800/6800/8800 systems; **cobas**® HIV-1 Quantitative nucleic acid test for use on the **cobas**® 5800/6800/8800 systems
Establishment Registration	Roche Molecular Systems, Inc. (2243471)

1. DEVICE DESCRIPTION

cobas® HIV-1/HIV-2 Qualitative

cobas® HIV-1/HIV-2 Qualitative is based on fully automated sample preparation (nucleic acid extraction and purification) followed by PCR amplification and detection. The **cobas**® 5800 system is designed as one integrated instrument. The **cobas**® 6800/8800 systems consist of the sample supply module, the transfer module, the processing module, and the analytic module. Automated data management is performed by the **cobas**® 5800 or **cobas**® 6800/8800 systems software which assigns test results for all tests as non-reactive, reactive, or invalid. Results can be reviewed directly on the system screen, exported, or printed as a PDF report.

Nucleic acid from patient samples and added armored RNA internal control (IC) molecules (which serve as the sample preparation and amplification/detection process control) is simultaneously extracted. In addition, the test utilizes three external controls: two positive and one negative control. In summary, viral nucleic acid is released by addition of proteinase and lysis reagent to the sample. The released nucleic acid binds to the silica surface of the added magnetic glass particles. Unbound substances and impurities, such as denatured protein, cellular debris and potential PCR inhibitors are removed with subsequent wash steps and purified nucleic acid is eluted from the magnetic glass particles with elution buffer at elevated temperature.

Selective amplification of target nucleic acid from the sample is achieved by the use of target virus-specific forward and reverse primers which are selected from highly conserved regions of the HIV-1 and HIV-2 genomes. The HIV-1 gag gene, the HIV-1 LTR region (dual target for HIV-1) and HIV-2 LTR region are amplified by **cobas**® HIV-1/HIV-2 Qualitative.

Selective amplification of IC is achieved by the use of sequence-specific forward and reverse primers which are selected to have no homology with the HIV-1 or HIV-2 genomes. A thermostable deoxyribonucleic acid (DNA) polymerase enzyme is used for both reverse-transcription and PCR amplification. The target and IC sequences are amplified simultaneously utilizing a universal PCR amplification profile with predefined temperature steps and number of cycles. The master mix includes deoxyuridine triphosphate (dUTP), instead of deoxythimidine triphosphate (dTTP), which is incorporated into the newly synthesized DNA (amplicon).[1-3] Any contaminating amplicons from previous PCR runs are eliminated by the AmpErase enzyme, which is included in the PCR master mix, during the first thermal cycling step. However, newly formed amplicons are not eliminated since the AmpErase enzyme is inactivated once exposed to temperatures above 55°C.

cobas® HIV-1/HIV-2 Qualitative master mix contains two detection probes specific for the HIV-1 target sequences, one for HIV-2 target sequences and one for the IC. The probes are labeled with target specific fluorescent reporter dyes allowing simultaneous detection of HIV-1 target, HIV-2 target and IC in three different target channels. When not bound to the target sequence, the fluorescent signal of the intact probes is suppressed by a quencher dye. During the PCR amplification step, hybridization of the probes to the specific single-stranded DNA template results in cleavage of the probe by the 5' to 3' exonuclease activity of the DNA polymerase resulting in separation of the reporter and quencher dyes and the generation of a fluorescent signal. With each PCR cycle, increasing amounts of cleaved probes are generated and the cumulative signal of the reporter dye increases concomitantly. Real-time detection and discrimination of PCR products is accomplished by measuring the fluorescence of the released reporter dyes for the viral targets and IC, respectively.

cobas® HIV-1

cobas® HIV-1 is a quantitative test performed on the **cobas**® 5800 system, **cobas**® 6800 system and **cobas**® 8800 system. **cobas**® HIV-1 enables the detection and quantitation of HIV-1 RNA in EDTA plasma of infected patients. Two probes are used to detect and quantify, but not discriminate group M, N and O subtypes. The viral load is quantified against a non-HIV-1 armored RNA quantitation standard (RNA-QS), which is introduced into each specimen during sample processing. The RNA-QS functions as an internal control to monitor the entire sample preparation and polymerase chain reaction (PCR) amplification process. In addition, the test utilizes three external controls: a high titer positive, a low titer positive, and a negative control.

cobas® HIV-1 is based on fully automated sample preparation (nucleic acid extraction and purification) followed by PCR amplification and detection. The **cobas**® 5800 system is designed as one integrated instrument. The **cobas**® 6800/8800 systems consist of the sample supply module, the transfer module, the processing module, and the analytic module. Automated data management is performed by the **cobas**® 5800 or **cobas**® 6800/8800 systems software (SW) which assigns test results for all tests as target not detected, < LLoQ (lower limit of quantitation), > ULoQ (upper limit of quantitation) or HIV-1 RNA detected, a value in the linear range LLoQ ≤ x ≤ ULoQ. Results can be reviewed directly on the system screen, exported, or printed as a report.

Nucleic acid from patient samples, external controls and added armored RNA (RNA-QS) molecules is simultaneously extracted. In summary, viral nucleic acid is released by addition of

proteinase and lysis reagent to the sample. The released nucleic acid binds to the silica surface of the added magnetic glass particles. Unbound substances and impurities, such as denatured protein, cellular debris and potential PCR inhibitors are removed with subsequent wash reagent steps and purified nucleic acid is eluted from the magnetic glass particles with elution buffer at elevated temperature.

Selective amplification of target nucleic acid from the sample is achieved by the use of target virus-specific forward and reverse primers which are selected from highly conserved regions of the HIV-1 genome. The HIV-1 group-specific antigen (gag) gene and the HIV-1 long terminal repeat (LTR) region (dual target) are amplified by **cobas**® HIV-1. Selective amplification of RNA-QS is achieved by the use of sequence-specific forward and reverse primers which are selected to have no homology with the HIV-1 genome. A thermostable DNA polymerase enzyme is used for both reverse-transcription and PCR amplification. The target and RNA-QS sequences are amplified simultaneously utilizing a PCR amplification profile with predefined temperature steps and number of cycles. The master mix includes deoxyuridine triphosphate (dUTP), instead of deoxythymidine triphosphate (dTTP), which is incorporated into the newly synthesized DNA (amplicon). Any contaminating amplicons from previous PCR runs are eliminated by the AmpErase enzyme, which is included in the PCR master mix, during the first thermal cycling step. However, newly formed amplicons are not eliminated since the AmpErase enzyme is inactivated once exposed to temperatures above 55°C.

The **cobas**® HIV-1 master mix contains two detection probes specific for the HIV-1 target sequences and one for the RNA-QS. The probes are labeled with target specific fluorescent reporter dyes allowing simultaneous detection of HIV-1 target and RNA-QS in two different target channels. When not bound to the target sequence, the fluorescent signal of the intact probes is suppressed by a quencher dye. During the PCR amplification step, hybridization of the probes to the specific single-stranded DNA template results in cleavage of the probe by the 5' to 3' exonuclease activity of the DNA polymerase resulting in separation of the reporter and quencher dyes and the generation of a fluorescent signal. With each PCR cycle, increasing amounts of cleaved probes are generated and the cumulative signal of the reporter dye increases concomitantly. Real-time detection and discrimination of PCR products is accomplished by measuring the fluorescence of the released reporter dyes for the viral targets and RNA-QS, respectively.

2. INDICATIONS FOR USE

cobas® HIV-1/HIV-2 Qualitative

cobas® HIV-1/HIV-2 Qualitative for use on the **cobas**® 5800/6800/8800 systems is an in vitro nucleic acid amplification test for the qualitative detection and differentiation of human immunodeficiency virus type 1 (HIV-1) and type 2 (HIV-2) RNA in human serum and plasma.

The test is intended to be used as an aid in diagnosis of HIV-1/HIV-2 infection. Detection of HIV-1 or HIV-2 nucleic acid is indicative of HIV-1 or HIV-2 infection, respectively. The presence of HIV-1 or HIV-2 nucleic acid in the plasma or serum of individuals without antibodies to HIV-1 or HIV-2 is indicative of acute or primary infection. The **cobas**® HIV-1/HIV-2 Qualitative may also be used as an additional test to confirm the presence of HIV-1 or HIV-2 infection in an individual with specimens reactive for HIV-1 or HIV-2 antibodies or antigens. The assay may also be used as an aid in the diagnosis of infection with HIV-1 and/or HIV-2 in pediatric subjects and pregnant women.

This assay is not intended to be used for monitoring patient status, or for screening donors of blood, plasma, or human cells, tissues, and cellular and tissue-based products (HCT/Ps) for HIV.

cobas® HIV-1

cobas® HIV-1 is an in vitro nucleic acid amplification test for the quantitation of human immunodeficiency virus type 1 (HIV-1) in EDTA plasma of HIV-1-infected individuals using the automated **cobas**® 5800/6800/8800 systems for specimen processing, amplification and detection. The test can quantitate HIV-1 RNA over the range of 20-10,000,000 cp/mL (33 to 1.67×10^7 International Units/mL).

This test is intended for use in conjunction with clinical presentation and other laboratory markers for the clinical management of HIV-1 infected patients. The test can be used to assess patient prognosis by measuring the baseline HIV-1 level or to monitor the effects of antiretroviral therapy by measuring changes in HIV-1 RNA levels during the course of antiretroviral treatment.

cobas® HIV-1 is not intended for use as a screening test for the presence of HIV-1 in donated blood or plasma or as a diagnostic test to confirm the presence of HIV-1 infection.

3. TECHNOLOGICAL CHARACTERISTICS

cobas® HIV-1/HIV-2 Qualitative is a nucleic acid amplification test intended for the qualitative detection and differentiation of human immunodeficiency virus type 1 (HIV-1) and type 2 (HIV-2) RNA in human serum and plasma.

cobas® HIV-1 is a nucleic acid amplification test intended for the quantitation of human immunodeficiency virus type 1 (HIV-1) in EDTA plasma of HIV-1-infected individuals. In this submission there are no changes to the assay reagents.

The purpose of this submission is to evaluate two material and design changes for the analytical cycler units of the cobas® 6800 and cobas 8800 systems in the candidate devices, changing the current (b) (4) to (b) (4) and changing the current (b) (4) to (b) (4) Minor typographical changes to the Instructions for Use and package labeling for the assays were also included in the submission.

The technical characteristics of the candidate device, **cobas**® HIV-1/HIV-2 Qualitative, are compared with the identified predicate device, **cobas**® HIV-1/HIV-2 Qualitative nucleic acid test for use on the **cobas**® 5800/6800/8800 systems (**cobas**® HIV-1/HIV-2 Qualitative) (BP190360) in Table 1.

The technical characteristics of the candidate device, **cobas**® HIV-1, are compared with the identified predicate device, **cobas**® HIV-1 Quantitative nucleic acid test for use on the **cobas**® 5800/6800/8800 systems (**cobas**® HIV-1) (BP150262) in Table 2.

Table 1: Similarities and Differences between cobas® HIV-1/HIV-2 Qualitative and the Predicate Device.

Comparator	Candidate Device: cobas® HIV-1/HIV-2 Qualitative	Predicate Device: cobas® HIV-1/HIV-2 Qualitative (BP190360, BK251233)
Proprietary Name	**cobas**® HIV-1/HIV-2 Qualitative Nucleic acid test for use on the **cobas**® 5800/6800/8800 systems	Same
Regulation Number	21 CFR 866.3957	Same
Regulation Name	Human immunodeficiency virus (HIV) nucleic acid (NAT) diagnostic and/or supplemental test	Same
Regulatory Class	Class II	Same
Product Code	QST	Same

Comparator	Candidate Device: **cobas® HIV-1/HIV-2 Qualitative**	Predicate Device: **cobas® HIV-1/HIV-2 Qualitative** **(BP190360, BK251233)**
Intended Use	**cobas®** HIV-1/HIV-2 Qualitative for use on the **cobas®** 5800/6800/8800 Systems is an in vitro nucleic acid amplification test for the qualitative detection and differentiation of human immunodeficiency virus type 1 (HIV-1) and type 2 (HIV-2) RNA in human serum and plasma. The test is intended to be used as an aid in diagnosis of HIV-1/HIV-2 infection. Detection of HIV-1 or HIV-2 nucleic acid is indicative of HIV-1 or HIV-2 infection, respectively. The presence of HIV-1 or HIV-2 nucleic acid in the plasma or serum of individuals without antibodies to HIV-1 or HIV-2 is indicative of acute or primary infection. The **cobas®** HIV-1/HIV-2 Qualitative may also be used as an additional test to confirm the presence of HIV-1 or HIV-2 infection in an individual with specimens reactive for HIV-1 or HIV-2 antibodies or antigens. The assay may also be used as an aid in the diagnosis of infection with HIV-1 and/or HIV-2 in pediatric subjects and pregnant women. This assay is not intended to be used for monitoring patient status, or for screening donors of blood, plasma, or human cells, tissues, and cellular and tissue-based products (HCT/Ps) for HIV.	Same
Conditions for use	For prescription use	Same
Sample Types	Human serum and plasma	Same
Subject Status	Individuals suspected of active HIV-1/HIV-2 infection	Same
Analyte Targets	HIV-1 HIV-2	Same
Sample Preparation Procedure	Automated by cobas 5800/6800/8800 systems	Same
Amplification Technology	Real-time PCR	Same
Detection Chemistry	Paired reporter and quencher fluorescence labeled probes (TaqMan Technology)	Same

Comparator	Candidate Device: **cobas® HIV-1/HIV-2 Qualitative**	Predicate Device: **cobas® HIV-1/HIV-2 Qualitative** **(BP190360, BK251233)**
Controls used	RNA Internal Control (internal control) **cobas®** HIV-1/HIV-2 Qualitative Control Kit (external positive control) **cobas®** NHP Negative Control Kit (external negative control)	Same
Instrument Platform	**cobas®** 5800/6800/8800 systems	Same
Amplification/Detection	Updated light source (LED) and Light Detection (Digital Camera) Real-time PCR using fluorescence signal detection. Separate detection and thermal cycler units/modules with specific temperatures and times for denaturation, annealing, and elongation steps, result calculation and interpretation methods, and filter specifications	Same (except updated light source (LED) and Light Detection (Digital Camera))
Number of supported assays per run	6 assays/run	3 assays/run
Throughput: **cobas®** 6800 (1 analytical cycler) **cobas®** 6800 (2 analytical cycler) **cobas®** 8800 (4 analytical cycler)	 384 tests in 8 hours 480 tests in 8 hours 960 tests in 8 hours	 384 tests in 8 hours N/A 960 tests in 8 hours
High Level Instrument Software Architecture	Refactored and modularized instrument control (IC) SW module and instrument management (IM) SW module are combined in one SW module. The x800 Data Manager SW module will replace the IG SW Module. x800 ASAP SW will replace the **cobas®** 6800/8800 ASAP and cobas® 5800 ASAP. **cobas®** 5800 system with software version 1.0 (P/N 08707464001), and the **cobas®** 6800/8800 systems with software version 2.0 (P/N 09575154001 and P/N 09575146001)	Instrument Control (IC) SW Instrument Management (IM) SW Instrument Gateway (IG) SW **cobas®** 6800/8800 Assay-specific analysis packages (ASAP) SW **cobas®** 6800/8800 systems with software version 1.4 (P/N 05524245001 or P/N 05412722001) **cobas®** 5800 Assay-specific analysis packages (ASAP) SW **cobas®** 5800 system with software version 1.0 (P/N 08707464001)

Comparator	Candidate Device: **cobas® HIV-1/HIV-2 Qualitative**	Predicate Device: **cobas® HIV-1/HIV-2 Qualitative** **(BP190360, BK251233)**
Analytic Cycler/Thermal unit	(b) (4) Heating Element (b) (4) Sensors Printed Circuit Board Assembled (PCBA) Block Controller. Introduces sensor redundancy, only 3 out of 6 sensors must be functional	(b) (4) Heating Element (b) (4) Sensors Printed Circuit Board Assembled (PCBA) Block Interface and PCBA Block Control. One failed sensor requires whole unit replacement.
Analytic Cycler/Photometer module detection unit	(b) (4) Material: (b) (4) Mechanical Design: (b) (4)	(b) (4) Material: (b) (4) Mechanical Design: (b) (4)
Control Scheduling	Default setting will remain the same as **cobas®** HIV-1/2 Qualitative Additional setting possible for alternate control frequency based on lab requirements and local regulations Note: - Controls will be required at least for each reagent lot change and every 72 hours. - The new control concept is identical to the one with **cobas®** ® 5800 system.	Positive control and negative control included on every amplification/detection plate

Table 2: Similarities and Differences between cobas® HIV-1 and the Predicate Device.

Comparator	Candidate Device: **cobas® HIV-1**	Predicate Device: **cobas® HIV-1** **(BP150262, BK251235)**
Proprietary Name	**cobas®** HIV-1 Quantitative nucleic acid test for use on the **cobas®** 5800/6800/8800 systems	Same

Comparator	Candidate Device: **cobas® HIV-1**	Predicate Device: **cobas® HIV-1** **(BP150262, BK251235)**
Regulation Number	21 CFR 866.3958	Same
Regulation Name	Human immunodeficiency virus (HIV) viral load monitoring test	Same
Regulatory Class	Class II	Same
Product Code	QUM	Same
Intended Use	**cobas®** HIV-1 is an in vitro nucleic acid amplification test for the quantitation of human immunodeficiency virus type 1 (HIV-1) in EDTA plasma of HIV-1-infected individuals using the automated **cobas®** 5800/6800/8800 systems for specimen processing, amplification and detection. The test can quantitate HIV-1 RNA over the range of 20-10,000,000 cp/mL (33 to 1.67 x 10^7 International Units/mL). This test is intended for use in conjunction with clinical presentation and other laboratory markers for the clinical management of HIV-1 infected patients. The test can be used to assess patient prognosis by measuring the baseline HIV-1 level or to monitor the effects of antiretroviral therapy by measuring changes in HIV-1 RNA levels during the course of antiretroviral treatment. **cobas®** HIV-1 is not intended for use as a screening test for the presence of HIV-1 in donated blood or plasma or as a diagnostic test to confirm the presence of HIV-1 infection.	Same
Conditions for use	For prescription use	Same
Sample Types	EDTA plasma	Same
Subject Status	HIV-infected individuals	Same
Analyte Targets	HIV-1	Same
Sample Preparation Procedure	Automated by cobas 5800/6800/8800 systems	Same
Amplification Technology	Real-time PCR	Same
Detection Chemistry	Paired reporter and quencher fluorescence labeled probes (TaqMan Technology)	Same

Comparator	Candidate Device: **cobas® HIV-1**	Predicate Device: **cobas® HIV-1** **(BP150262, BK251235)**
Controls used	RNA Quantitation Standard (RNA-QS) (internal control) **cobas®** HBV/HCV/HIV-1 Control Kit (external positive control) **cobas®** NHP Negative Control Kit (external negative control)	Same
Instrument Platform	**cobas®** 5800/6800/8800 systems	Same
Amplification/Detection	Updated light source (LED) and Light Detection (Digital Camera) Real-time PCR using fluorescence signal detection. Separate detection and thermal cycler units/modules with specific temperatures and times for denaturation, annealing, and elongation steps, result calculation and interpretation methods, and filter specifications	Same (except updated light source (LED) and Light Detection (Digital Camera))
Number of supported assays per run	6 assays/run	3 assays/run
Throughput: **cobas®** 6800 (1 analytical cycler) **cobas®** 6800 (2 analytical cycler) **cobas®** 8800 (4 analytical cycler)	 384 tests in 8 hours 480 tests in 8 hours 960 tests in 8 hours	 384 tests in 8 hours N/A 960 tests in 8 hours
High Level Instrument Software Architecture	Refactored and modularized instrument control (IC) SW module and instrument management (IM) SW module are combined in one SW module. The x800 Data Manager SW module will replace the IG SW Module. x800 ASAP SW will replace the **cobas®** 6800/8800 ASAP and **cobas®** 5800 ASAP. cobas® 5800 system with software version 1.0 (P/N 08707464001), and the cobas® 6800/8800 systems with software version 2.0 (P/N 09575154001 and P/N 09575146001)	Instrument Control (IC) SW Instrument Management (IM) SW Instrument Gateway (IG) SW **cobas®** 6800/8800 Assay-specific analysis packages (ASAP) SW **cobas®** 6800/8800 systems with software version 1.4 (P/N 05524245001 or P/N 05412722001) **cobas®** 5800 Assay-specific analysis packages (ASAP) SW cobas® 5800 system with software version 1.0 (P/N 08707464001)

Comparator	Candidate Device: **cobas® HIV-1**	Predicate Device: **cobas® HIV-1** **(BP150262, BK251235)**
Analytic Cycler/Thermal unit	(b) (4) Heating Element (b) (4) Sensors Printed Circuit Board Assembled (PCBA) Block Controller. Introduces sensor redundancy, only 3 out of 6 sensors must be functional.	(b) (4) Heating Element (b) (4) Sensors Printed Circuit Board Assembled (PCBA) Block Interface and PCBA Block Control. One failed sensor requires whole unit replacement.
Analytic Cycler/Photometer module detection unit	(b) (4) Material: (b) (4) Mechanical Design: (b) (4)	(b) (4) Material: (b) (4) Mechanical Design: (b) (4)
Control Scheduling	Default setting will remain the same as the predicate device Additional setting possible for alternate control frequency based on lab requirements and local regulations Note: - Controls will be required at least for each reagent lot change and every 72 hours. - The new control concept is identical to the one with **cobas®** 5800 system.	Positive control and negative control included on every amplification/detection plate

4. NON-CLINICAL PERFORMANCE EVALUATION

Analytical studies for the **cobas®** HIV-1/HIV-2 and **cobas®** HIV-1 were completed as part of BP190360 and BP150262, respectively, and no new analytical studies were performed because the assay reagents for these devices have not changed.

To confirm system performance equivalency between the candidate **cobas**® HIV-1/HIV-2 Qualitative and the predicate device, system equivalency studies were performed with the qualitative cobas MPX as a representative assay and were reviewed for approval in BL125576/127.

For the **cobas**® HIV-1, system equivalency studies were performed with the quantitative **cobas**® HCV as a representative assay and were reviewed for clearance in K252484.

5. CLINICAL PERFORMANCE EVALUATION

Clinical studies were completed as part of BP190360 for the **cobas**® HIV-1/HIV-2 Qualitative and completed as part of BP150262 for the **cobas**® HIV-1. There are no changes to the assay reagents, and therefore, no additional clinical studies were performed in support of the hardware changes described herein.

6. CONCLUSIONS

As the **cobas**® HIV-1/HIV-2 Qualitative and the **cobas**® HIV-1 assay reagents and intended use population have not changed, additional clinical studies were not performed. Non-clinical studies were conducted to evaluate the performance of the **cobas**® HIV-1/HIV-2 Qualitative Assay and the **cobas**® HIV-1 Quantitative nucleic acid test on the updated **cobas**® 6800/8800 systems, and the results demonstrated that the devices are as safe, as effective, and perform as well as the predicates.