Date: 5 November 2014

Final Report
WHO evaluation of Diagnostic Kit for Antibody to Human Immunodeficiency Virus (1+2) (Colloidal Gold) (3 Lines) (whole blood, serum/plasma)

(Newscen Coast Bio-Pharmaceutical Co., Ltd.)

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Prequalification of In Vitro Diagnostics programme
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1. Details of the product

1.1. Name of product

A qualitative rapid diagnostic test for the detection of HIV-1/2 antibodies in human serum, plasma and whole blood

1.2. Manufacturer

Newscen Coast Bio-Pharmaceutical Co., Ltd.
Address:
65 THE 6 TH Street, TEDA
TIANJIN, 300457
PR China
Tel: + 86 22 2532 1648
Fax: + 86 22 25328062
Corporate web site: www.newscen.com

1.3. Indicative price per test and product codes

Product code	Contents of the test kit	Indicative price in operating currency
G1 HIV3-223 / G1 HIV3-233	25 tests Diluent (5 ml) and pipettes	US$ 0.58 per test
G1 HIV3-223 / G1 HIV3-233	40tests Diluent (5 ml) and pipettes	US$ 0.58 per test

2. General information about the product

2.1. Type (format) of assay

Lateral flow immunochromatographic rapid diagnostic test

2.2. Type of antigen

Recombinant proteins HIV-1 gp 120 and gp 41 and HIV-2 gp 36

2.3. Type of solid phase

Nitrocellulose membrane.

2.4. Contents of test kit

The product is available in pack sizes of 25 and 40 tests. For this performance evaluation, the 25 test pack size was evaluated. Each test kit contains disposable plastic pipettes, devices, diluent buffer bottle and instructions for use (package insert).

2.5. Test kit controls

Test kit controls:
Test kit controls (for anti-HIV-1/2) were not supplied in the test kit.

Specimen/reagent addition control:

The control line appears when only buffer is added to the device (without specimen) and is therefore a reagent addition control.

2.6. Conjugate (and diluent)

Conjugate: colloidal gold particles labeled with specific HIV (1+2) antigens.
Conjugate diluent: not applicable.

2.7. Substrate (and diluent)

Substrate: not applicable.
Substrate diluent: not applicable.

2.8. Test kit dimensions (width-length-height)

The dimensions of the pack size of 25 tests are 16-12.5-6.5 cms.
The dimensions of the pack size of 40 tests are 25-12.5-6.5 cms.

2.9. Labels

All reagents and devices were clearly labelled. The product code, lot number and expiry date were included on the outer packaging (test kit box) and most of individual components including test pouches and buffer vial. The product name was stated on the test device.

2.10. Quantity of reagents

All reagents were supplied in sufficient quantities for the serum/plasma test procedure.

2.11. Instructions for use

Most of the instructions for use (package insert) were clear. The test procedure including specimen collection, specimen storage and result interpretation was clear. In the instructions for use, it states that the result must be observed 5-15 minutes after adding the assay diluent.

In the instructions for sample collection and preparation, it states that when finger stick whole blood will be used about 100 µl of whole blood must be obtained. However in the assay procedure it states that one drop of sample must be added to the device.

2.12. Storage conditions

The product must be stored at 4-30 °C.

2.13. Shelf life

According to the manufacturer, the shelf life of the product upon manufacture is 24 months. The guaranteed shelf life upon delivery must be negotiated during the procurement process.

3. Operational aspects of the product

3.1. Reagents

Not applicable.

3.1.1. Stability after opening/preparation (°C)

All components are stable until the expiry date when stored at 2-30°C.

3.2. Specimens

3.2.1. Specimen type

This product is intended for use with serum/plasma, and capillary whole blood specimens. For this performance evaluation, serum/plasma specimens were used and were delivered using a transfer pipette provided within the test kit. EDTA, citrate or heparin may be used as anticoagulants.

3.2.2. Specimen volume

35 µl (one drop) of specimen was required to perform the assay.

3.2.3. Number of specimens per run

Minimum number of specimens per run: 1
Maximum number of specimens per run: 10

3.3. Incubation temperature

15-25 °C.

3.4. Washing procedure

Not applicable.

3.5. Reading procedure

The results were read visually according to the instructions for use. In addition, the intensity of each test band was scored and entered into the data collection sheet.

3.6. Time required to perform the assay (h:min)

Time to test one specimen: 0:06
Time to test one run (e.g. 10 specimens): 0:07

3.7. Equipment and consumables required but not provided in the test kit

The following equipment was required but not provided:
For capillary whole blood specimens: micropipette.

The following consumables were required but not provided:
For capillary whole blood specimens: alcohol swabs, lancets.
For venous whole blood and serum/plasma specimens: blood collection equipment

4. Materials and methods

4.1. Specimens

4.1.1. WHO HIV specimen reference panel

The panel consisted of approximately 1117 clinically-derived serum/plasma specimens of European, African, Latin America and Asian origin, see Table 1. There were 460 anti-HIV positive specimens, of which 16 are anti-HIV-2 positive and 657 anti-HIV negative specimens.

Table 1 - WHO Specimen Evaluation Panel

HIV positive specimens	HIV negative specimens	Total number
460	657	1117

4.1.2. Lot-to-lot variation panel

Lot to lot variation was assessed on two separate production lots using a panel of ten anti-HIV positive specimens diluted in 2-fold dilutions to make 16 member dilution series (n=160).

4.1.3. HIV seroconversion panels

Eight HIV seroconversion panels: PRB914, PRB925, PRB926, PRB930, PRB955, PRB965, PRB968, PRB 969 (sourced from SeraCare Life Science Inc) were tested in singular on one production lot.

4.1.4. HIV mixed titer panel

One anti-HIV mixed titer performance panel containing 25 members: PRB205 (sourced from SeraCare Life Science Inc) was tested in singular on one production lot.

4.1.5. WHO reference preparations

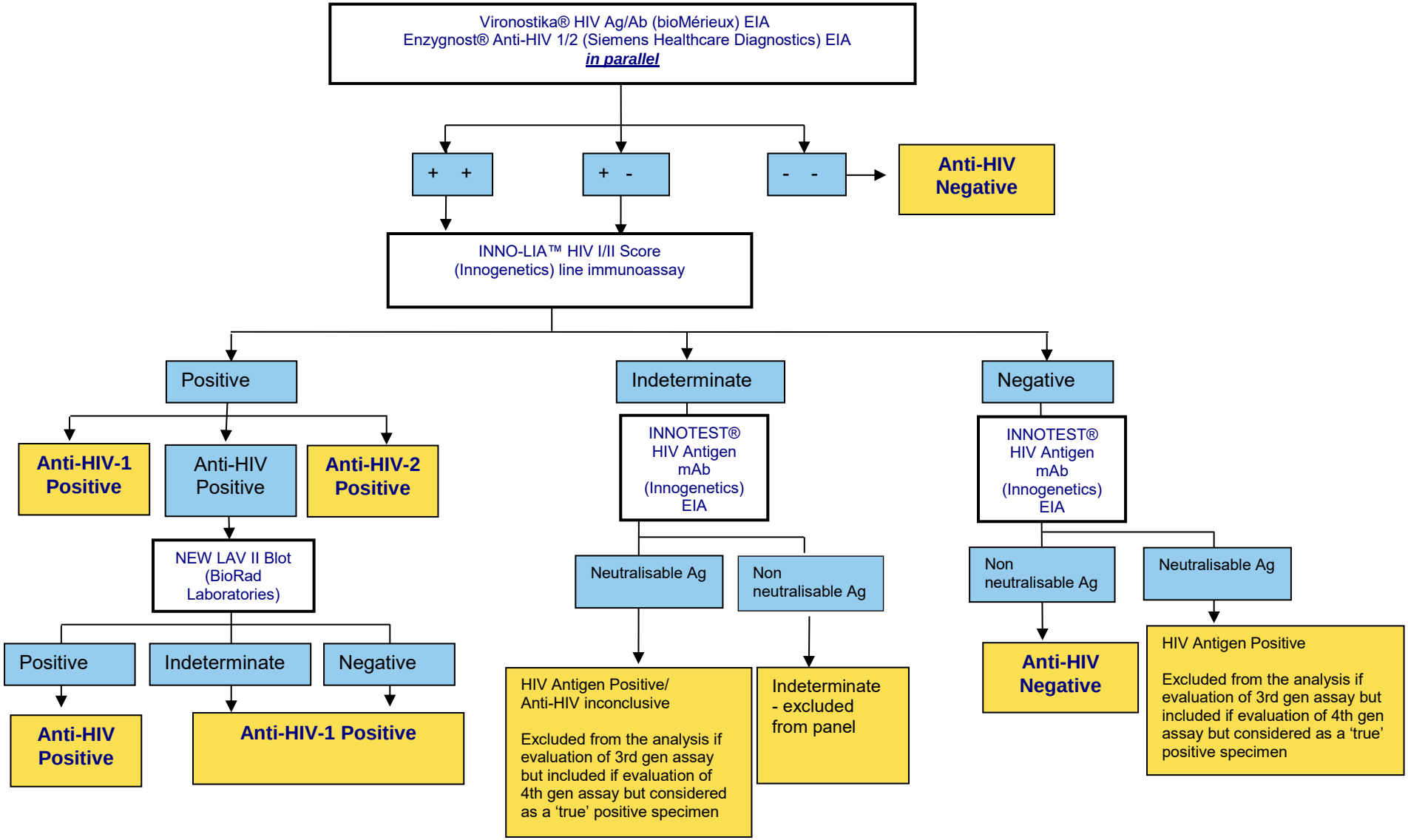
The WHO international biological reference preparation panel with the catalogue number 02/210 (Anti-HIV antibodies [HIV-1 subtypes A, B, C, CRF01_AE, group O and HIV-2] was tested in singular on one production lot.

4.1.6. External quality control specimen

An appropriate external quality control specimen was tested at the beginning of each testing session. The QC specimen was sourced by ITM according to their procedures.

4.2. Reference results

The WHO HIV specimen reference panel was characterized according to a standard combination of assays i.e. a standardized testing algorithm. These reference testing results were used to determine the true HIV status of each specimen for the purpose of this performance evaluation, see Figure 1.


Vironostika® HIV Ag/Ab (bioMérieux) EIA
Enzygnost® Anti-HIV 1/2 (Siemens Healthcare Diagnostics) EIA
in parallel
+ +
+ -
- -
Anti-HIV Negative
INNO-LIA™ HIV I/II Score (Innogenetics) line immunoassay
Positive
Indeterminate
Negative
Anti-HIV-1 Positive
Anti-HIV Positive
Anti-HIV-2 Positive
NEW LAV II Blot (BioRad Laboratories)
Positive
Indeterminate
Negative
Anti-HIV Positive
Anti-HIV-1 Positive
INNOTEST® HIV Antigen mAb (Innogenetics) EIA
Neutralisable Ag
Non neutralisable Ag
HIV Antigen Positive/ Anti-HIV inconclusive
Excluded from the analysis if evaluation of 3rd gen assay but included if evaluation of 4th gen assay but considered as a 'true' positive specimen
Indeterminate - excluded from panel
INNOTEST® HIV Antigen mAb (Innogenetics) EIA
Non neutralisable Ag
Neutralisable Ag
Anti-HIV Negative
HIV Antigen Positive
Excluded from the analysis if evaluation of 3rd gen assay but included if evaluation of 4th gen assay but considered as a 'true' positive specimen

Initially, each specimen was tested on the Vironostika HIV Ag/Ab (bioMérieux) EIA and Enzygnost Anti-HIV 1/2 Plus (Siemens Healthcare Diagnostics) EIA in parallel.

Specimens that are non-reactive on both EIAs were assigned anti-HIV negative.

Specimens with discrepant EIA results AND with dually reactive results on both EIAs were tested on the INNO-LIA™ HIV I/II Score (Innogenetics) line immunoassay. Specimens that were negative by line immunoassay were further tested on Innotest® HIV Antigen mAb (Innogenetics) EIA and if found non-reactive they were assigned anti-HIV negative. If found to be neutralisable for HIV-1 antigen, the specimen was considered HIV-1 antigen positive and anti-HIV negative and was retained for the evaluation of 4th generation assay **but not** for 3rd generation assays.

Specimens that are indeterminate by line immunoassay were further tested on Innotest® HIV Antigen mAb (Innogenetics) EIA and if found non-reactive then were excluded from the panel. Specimens that were reactive for antigen (and were neutralisable) were assigned as HIV-1 antigen positive and anti-HIV inconclusive. These specimens were retained for the evaluation of 4th generation assay **but not** for 3rd generation assays.

Specimens that were positive by line immunoassay were assigned as anti-HIV-1 positive or anti-HIV-2 positive. Those specimens that could not be discriminated (i.e. anti-HIV positive) were further tested on the NEW LAV II Blot (BioRad Laboratories). Specimens that were indeterminate or negative by the NEW LAV II Blot were assigned as anti-HIV-1 positive. Specimens that were positive by the NEW LAV II Blot were assigned as anti-HIV positive.

All reference assays were interpreted according to IFU as given by the manufacturer. The data obtained with Diagnostic Kit for Antibody to Human Immunodeficiency Virus (1+2) (Colloidal Gold) were compared to the reference testing results. All data from reference testing is shown together with the results of the Diagnostic Kit for Antibody to Human Immunodeficiency Virus (1+2) (Colloidal Gold) results in Annexes 1 and 2.

4.3. Lot numbers and expiry dates of test kits

Lot number A: 201401201	Expiry date: 19/01/2016
Lot number B: 201312091	Expiry date: 08/12/2015

4.4. Interpretation of testing results

In this performance evaluation, 10 specimens were tested per run. The test procedure was performed by one laboratory technician; the results were read independently by three technicians.

4.4.1. Endpoint stability

The reading endpoint was not stated, for this performance evaluation the results were read 5 minutes after the specimen and diluent was added to the test device.

4.4.2. Run validation

The criteria for result validation were in accordance with the instructions for use. The control band was visible for all test devices indicating all test devices were valid. In addition, an external QC specimen was run at the beginning of each testing session.

5. Data analysis

5.1. Performance characteristics

The following methods were used to calculate the performance characteristics, see Table 2.

Table 2. Calculation of performance characteristics

	Reference testing results			
Results of assay under evaluation		Reactive	Non-reactive	Total
	Reactive	a (true positives)	b (false positives)	a + b
	Non-reactive	c (false negatives)	d (true negatives)	c + d
	Total	a + c	b + d	a+b+c+d

5.1.1. Sensitivity

Sensitivity is the ability of the assay under evaluation to detect correctly specimens that contains the analyte (reference assays positive). Thus sensitivity is the number of true positive sera identified by the assay under evaluation as positive (a), divided by the number of sera identified by the reference assays as positive (a+c), expressed as a percentage.

Sensitivity = $\frac{a}{a+c}$

5.1.2. Specificity

Specificity is the ability of the assay under evaluation to detect correctly specimens that do not contain the analyte (reference assays negative). Thus specificity is the number of true negative sera identified by the assay under evaluation as negative (d), divided by the number of sera identified by the reference assays as negative (b+d), expressed as a percentage.

Specificity = $\frac{d}{b+d}$

5.1.3. Confidence intervals

The 95% confidence intervals were calculated for values in order to assess the level of uncertainty introduced by sample size, etc. Exact 95% confidence intervals for binomial proportions were calculated from the F-distribution. (Armitage, 2002; Kirkwood, 2003]

5.1.4. Predictive values

The positive predictive value is the probability that when the test is reactive that the specimen does contain HIV-1/2 antibodies. PPVs were calculated using the formula.

PPV = $\frac{(prevalence)(sensitivity)}{(prevalence)(sensitivity)+(1-prevalence)(1-specificity)}$

The negative predictive value is the probability that when the test is negative that a specimen does not have antibodies to HIV. NPVs were calculated using the formula.

$$\text{NPV} = \frac{(1-\textit{prevalence})(\textit{specificity})}{(1-\textit{prevalence})(\textit{specificity})+(\textit{prevalence})(1-\textit{sensitivity})}$$

The probability that a test result will accurately determine the true infection status of a person being tested varies with the prevalence of HIV infection in the population from which the person comes. In general, the higher the prevalence of HIV infection in the population, the greater the probability that a person testing positive is truly infected (i.e., the greater the positive predictive value [PPV]). Thus, with increasing prevalence, the proportion of individuals testing false-positive decreases; conversely, the likelihood that a person whose test result is negative is truly uninfected (i.e., the negative predictive value [NPV]), decreases as prevalence increases.

The PPV and NPV are calculated at a prevalence of 0.1%, 1% and 5%.

5.2. Indeterminate results

For the WHO specimen reference panel only: specimens which were found to be indeterminate by the criteria stated in the instructions for use were retested in duplicate on the same lot number of assay. In the case that the testing result could not be resolved after all testing, the specimen was called indeterminate and included in sensitivity/specificity calculations.

Values for initial sensitivity and specificity were calculated based on the results obtained for the assay under evaluation on the first lot. The final sensitivity and specificity values were calculated taking into consideration the repeat testing performed on the same lot and further testing on the second lot of the assay under evaluation.

5.3. Invalid results

Invalid test results were calculated based on testing with all specimen panels as the number of initial invalid test results as a proportion of test devices run using clinical specimens (WHO specimen reference panel only). Invalid results may mean invalid test results as defined by the instructions for use where the control line/band/spot does not appear or invalid due to obviously defective test device or defective transfer pipette.

5.4. Discrepant results

For the WHO specimen reference panel only: those specimens with results that were consistent with the reference testing results, underwent no further testing. Those specimens with results discrepant from the reference result were retested in duplicate using the same lot number by the same operator. The results that occurred two out of three times were recorded as the result for that particular lot. If the result was again discrepant, the specimen was repeated on the second lot, if available. If the result on the second lot was concordant with the reference testing results, no further testing was required. If the result was still discrepant from the reference results, the result was recorded as such.

The values for initial sensitivity and specificity were calculated based on the first results obtained for Diagnostic Kit for Antibody to Human Immunodeficiency Virus (1+2) (Colloidal Gold) on the first lot. The final sensitivity and specificity were calculated taking into consideration the repeat testing performed on a same lot and further testing second lot. The results of any discrepant results are presented in Annex 3

5.5. Interpretation of results from lot-to-lot panel

The results of the lot-to-lot variation panel on the two lots by Diagnostic Kit for Antibody to Human Immunodeficiency Virus (1+2) (Colloidal Gold) was compared and a variation of +/- 1 dilution series was considered acceptable. The results are presented in Annex 4.

5.6. Interpretation of results from HIV seroconversion panels

The results obtained with seroconversion panels from individuals in the early stages of HIV infection from Diagnostic Kit for Antibody to Human Immunodeficiency Virus (1+2) (Colloidal Gold) were compared with those results obtained using Enzygnost Anti-HIV 1/2 Plus (Siemens Healthcare Diagnostics), the assay arbitrarily designated the reference for determination of relative sensitivity in these panels. For each seroconversion panel, the first specimen in the sample sequence to become reactive with Enzygnost Anti-HIV 1/2 Plus was assigned the value “0”. Results from Diagnostic Kit for Antibody to Human Immunodeficiency Virus (1+2) (Colloidal Gold) were compared with Enzygnost Anti-HIV 1/2 Plus by determining the difference between the specimen assigned value “0” and the relative position in the sample sequence of the first specimen which showed a reactive result with the assay under evaluation. For example, if the assay became reactive two specimens earlier in a panel than Enzygnost Anti-HIV 1/2 Plus, the value assigned for that series in the assay was -2. Similarly, if an assay became reactive one specimen later than Enzygnost Anti-HIV 1/2 Plus, the value assigned was +1. The assigned values over the eight seroconversion panels were averaged to determine a mean relative seroconversion sensitivity index for Diagnostic Kit for Antibody to Human Immunodeficiency Virus (1+2) (Colloidal Gold) and the 95% confidence intervals were determined. All specimens were also tested on the Vironostika HIV Ag/Ab (bioMérieux) EIA, INNOTEST HIV Antigen mAb (Innogenetics) EIA and INNO-LIA HIV I/II Score (Innogenetics) line immunoassay. The results are presented in Annex 5.

5.7. Interpretation of results from HIV mixed titer panel

The number of specimens detected by Diagnostic Kit for Antibody to Human Immunodeficiency Virus (1+2) (Colloidal Gold) on the HIV mixed titer performance panel was determined by comparison with the expected results following interpretation of the combined reference testing results generated by the following assays: Enzygnost Anti-HIV 1/2 Plus (Siemens Healthcare Diagnostics) EIA, Vironostika® HIV Ag/Ab (bioMérieux) EIA, INNO-LIA™ HIV I/II Score (Innogenetics) line immunoassay, and INNOTEST® HIV Antigen mAb (Innogenetics) EIA. The results are presented in Annex 6.

5.8. Interpretation of results from WHO reference preparations

The number of specimens detected by Diagnostic Kit for Antibody to Human Immunodeficiency Virus (1+2) (Colloidal Gold) for the WHO biological reference preparation panel (1st International Reference Panel for anti-HIV [NIBSC code 02/210]) was determined by comparison with the expected results following interpretation of the combined reference testing results generated by the following assays: Enzygnost Anti-HIV 1/2 Plus (Siemens Healthcare Diagnostics) EIA, Vironostika® HIV Ag/Ab (bioMérieux) EIA, INNO-LIA™ HIV I/II Score (Innogenetics) line immunoassay, and INNOTEST® HIV Antigen mAb (Innogenetics) EIA. The results are presented in Annex 7.

5.9. Inter-reader variability

Three individuals independently interpreted each test result. The inter-reader variability was expressed as the percentage of specimens for which initial test results were differently interpreted (i.e. reactive, non-reactive, indeterminate) by the independent readers. The results are presented in Annex 8.

6. Results

6.1. Validation of results

All test runs were valid based on the run validation criteria outlined in the instructions for use. The red band in the control region (C) appeared at all test devices.

6.2. Comparison of initial testing results with reference results

6.2.1. Detection of antibodies to HIV-1/2

		Reference testing results			
		HIV-1 +	HIV-2	HIV -	Total
Diagnostic Kit for Antibody to Human imunodeficiency Virus (1+2) (Colloidal Gold) Initial results	HIV+ (region 1)	331	11	0	342
	HIV+ (region 2)	108	10	0	118
	HIV -	0	0	657	657
	Total	439	21	657	1117

Sensitivity (95% CI): 460/460 = 100% (99.2%-100%)
Specificity (95% CI): 657/657 = 100% (99.4%-100%)
Indeterminate results: 0/1117 = 0%
False positive results: 0/1117 = 0% (see Annex 3)
False negative results: 0/1117 = 0% (see Annex 3)

Among 439 HIV-1 seropositive specimens, 108 (24.6%) had a band in region 2 (HIV+), while among 21 HIV-2 seropositive specimens, 11 (52.4%) had a band in the region 1 (HIV+).

6.3. Comparison of final testing results with reference results

6.3.1. Detection of antibodies to HIV-1/2

		Reference testing results			
		HIV-1 +	HIV-2	HIV -	Total
Diagnostic Kit for Antibody to Human imunodeficiency Virus (1+2) (Colloidal Gold) Final results	HIV+ (region 1)	331	11	0	342
	HIV+ (region 2)	108	10	0	118
	HIV -	0	0	657	657
	Total	439	21	657	1117

Sensitivity (95% CI): 460/460 = 100% (99.2%-100%)
Specificity (95% CI): 657/657 = 100% (99.4%-100%)
Indeterminate results: 0/1117 = 0%
False positive results: 0/1117 = 0% (see Annex 3)
False negative results: 0/1117 = 0% (see Annex 3)

Among 439 HIV-1 seropositive specimens, 108 (24.6%) had a band in region 2 (HIV+), while among 21 HIV-2 seropositive specimens, 11 (52.4%) had a band in the region 1 (HIV+).

6.4. Discrepant results

No specimens showed a discrepant result.

The results are presented in Annex 3.

6.5. Predictive values

PPV (0.1% prevalence): 100%
PPV (1% prevalence) : 100%
PPV (5% prevalence) : 100%

NPV (0.1% prevalence): 100%
NPV (1% prevalence) : 100%
NPV (5% prevalence) : 100 %

6.6. Results from lot-to-lot panel

Variation was observed between lots 201401201 and 201312091 of Diagnostic Kit for Antibody to Human Immunodeficiency Virus (1+2) (Colloidal Gold). However this variation was within the acceptance range. The results are presented in Annex 4.

6.7. Results from HIV seroconversion panels

The mean seroconversion index was +0.125 specimens compared to the benchmark assay, a HIV-1/2 antibody detection assay; Enzygnost Anti-HIV 1/2 Plus Siemens Healthcare Diagnostics) EIA. Thus Diagnostic Kit for Antibody to Human Immunodeficiency Virus (1+2) (Colloidal Gold) detected HIV-1/2 antibodies in 8 different seroconversion panels, on average, 0.125 specimens later than the benchmark assay. The results are presented in Annex 5

6.8. Results from HIV mixed titer panel

The Diagnostic Kit for Antibody to Human Immunodeficiency Virus (1+2) (Colloidal Gold) did not detect the anti-HIV negative/HIV-1 antigen positive specimen. The Diagnostic Kit for Antibody to Human Immunodeficiency Virus (1+2) (Colloidal Gold) detected all other specimens of the HIV mixed titer panel in comparison with the expected results The results are presented in Annex 6.

6.9. Results from WHO reference preparations

The Diagnostic Kit for Antibody to Human Immunodeficiency Virus (1+2) (Colloidal Gold) detected all HIV-1 group M subtypes and HIV-2 contained in 1st International Reference Panel for anti-HIV [NIBSC code 02/210]. The HIV-1 group O specimen was not detected. The results are presented in Annex 7.

6.10. Inter-reader variability

The inter-reader variability was calculated and found to be:
HIV-1 band 0.45%
HIV-2 band 3.58%
HIV-1/2 band 4.03%
The results are presented in Annex 8.

7. Appraisal by laboratory technician

	Rating*	1	2	3	4	5
Kit instructions:	Clarity		✓			
	Presentation			✓		
	Content		✓			
	Safety instructions			✓		
Kit/reagent packaging and labelling	Clear				✓	
	Labelling				✓	
	Safety				✓	
Specimen dispensing and volume	Specimen type used	Serum/plasma				
	Specimen volume	35 µL				
	Specimen addition control					
Reagent dispensing	Reagent addition control	Yes				
Equipment required	Equipment required	Yes (for whole blood)				
	Details of equipment required	Optional: Precision pipette, tips.				
Number of steps to completion of test:	Number	2				
Endpoint stability:	Time	Not stated				
Time from start to completion:	Time	6 min				
Recommended maximum tests per run:	Test maximum	Not stated				
Actual number of tests possible per run:	Test number	10				

Other comments: In the assay procedure is written "use one foil pouch/test/sample", this is not clear. Sample must be completely been absorbed before adding the diluent buffer; it is not stated within which time the sample should be absorbed. The precise reading time is not provided.

* Rating key: : 1 = poor; 2 = needs improvement; 3 = satisfactory; 4 = good; 5 = excellent

8. Summary

Diagnostic Kit for Antibody to Human Immunodeficiency Virus (1+2) (Colloidal Gold) (Newscen Coast Bio-Pharmaceutical Co., Ltd.) was evaluated by WHO in the third quarter of 2014 using serum/plasma specimens. From this evaluation, we drew the following conclusions:

Diagnostic Kit for Antibody to Human Immunodeficiency Virus (1+2) (Colloidal Gold) (Newscen Coast Bio-Pharmaceutical Co., Ltd.) is a lateral flow immunochromatographic assay for the detection of HIV-1/2 antibodies in human serum/plasma and whole blood specimens. A volume of 35 µL of serum/plasma specimen is needed to perform the assay. When whole blood is used, a volume of 100 µl is required. This type of assay requires no sophisticated equipment and can therefore be performed in laboratories with limited facilities. However, the requirement of 100 µl of whole blood is a significant limitation especially when used in non-laboratory settings. Reading of the results can be done visually i.e. subjectively read.

In this limited evaluation on a panel of 1117 clinically-derived specimens, we found an initial sensitivity (95% CI) of 100% (99.2% - 100%) and an initial specificity (95% CI) of 100% (99.4% - 100%) compared to the reference assays. The final sensitivity (95% CI) was 100% (99.2% - 100%) and the final specificity (95% CI) was 100% (99.4% - 100%) compared to the reference assays. Lot to lot variation was acceptable. However Diagnostic Kit for Antibody to Human Immunodeficiency Virus (1+2) (Colloidal Gold) assay showed significant cross reactivity; among 439 HIV-1 seropositive specimens, 108 (24.6%) had a band in region 2, while among 21 HIV-2 seropositive specimens, 11 (52.4%) had a band in the region 1.

For eight seroconversion panels, Diagnostic Kit for Antibody to Human Immunodeficiency Virus (1+2) (Colloidal Gold) detected on average 0.125 specimens later than the benchmark assay; Enzygnost Anti-HIV 1/2 Plus (Siemens Healthcare Diagnostics).

For the mixed titer panel, Diagnostic Kit for Antibody to Human Immunodeficiency Virus (1+2) (Colloidal Gold) could not detect one anti-HIV negative/HIV-1 antigen positive specimen. All other panel members were correctly identified.

For the 1st International Reference Panel for anti-HIV [NIBSC code 02/210], Diagnostic Kit for Antibody to Human Immunodeficiency Virus (1+2) (Colloidal Gold) did not detect the HIV-1 group O specimen; all other specimens were detected.

In this study, 0% of the results were recorded as indeterminate. Results were interpreted independently by three technicians; the inter-reader variability was 4.03% (0.45% for HIV-1 and 3.58% for HIV-2). The invalid rate was 0%.

If Diagnostic Kit for Antibody to Human Immunodeficiency Virus (1+2) (Colloidal Gold) successfully meet all WHO prequalification requirements a summary of this data will be published by the WHO Prequalification of In Vitro Diagnostics Programme in the WHO Public Report for Diagnostic Kit for Antibody to Human Immunodeficiency Virus (1+2) (Colloidal Gold) (Newscen Coast Bio-Pharmaceutical Co., Ltd.). The detailed data of this evaluation will be published in a WHO report of the operational characteristics of commercially available assays to detect HIV-1/2 antibodies in human serum/plasma. These reports will be made available on the WHO web site at: http://www.who.int/diagnostics_laboratory/publications/en/ and http://www.who.int/diagnostics_laboratory/evaluations/PQ_list/en/index.html

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10. Diagnostic Kit for Antibody to Human Immunodeficiency Virus (1+2) (Colloidal Gold)

Diagnostic Kit for Antibody to Human Immunodeficiency Virus (1+2) (Colloidal Gold) 3-Lines

【For the qualitative detection of HIV (1+2) antibodies in serum/plasma and whole blood】
(Single use test cassette)

Read this package insert completely before using the product. Follow the instructions carefully when performing the test. Not doing so may result in incorrect test results. Before performing testing, all operators MUST read and become familiar with Universal Precautions for Prevention of Transmission of Human immunodeficiency Virus, Hepatitis B Virus, and Other Blood-Borne Pathogens in Health-Care Settings.

NAME AND INTENDED USE

Diagnostic Kit for Antibody to Human Immunodeficiency Virus (1+2) (Colloidal Gold) is a single use rapid immunoassay, for the qualitative test for the detection of antibodies to Human Immunodeficiency Virus type 1 and 2 in human serum, plasma or whole blood. Diagnostic Kit for Antibody to Human Immunodeficiency Virus (1+2) (Colloidal Gold) is intended for use at point of care settings as an aid in diagnosis of infection with HIV-1 and HIV-2 virus.

Intended users are the hospital professionals. Professionals use this test in clinics and hospitals. They are Medical technologists, Nurses, or Doctors who use this product. They have certain knowledge and skills to perform the test safely.

It is considered as an initial screening test for HIV-1/2 antibodies. All positive specimens must be confirmed with Western Blot or other qualified ELISA test systems.

RESTRICTIONS

1. Sale of Diagnostic Kit for Antibody to Human Immunodeficiency Virus (1+2) (Colloidal Gold) is limited to clinical laboratories
   - who have an adequate quality assurance program, including planned systematic approach to provide adequate confidence so the quality will be met.
   - the operators will receive and use the instructional materials.
2. Diagnostic Kit for Antibody to Human Immunodeficiency Virus (1+2) (Colloidal Gold) is approved for use by clinical professionals.
3. The test subjects must receive the "Subject Information Leaflet" prior to specimen collection and appropriate information when test results are provided.

SUMMARY AND EXPLANATION OF THE TEST

It has been shown that the acquired immunodeficiency syndrome (AIDS) is caused by viruses transmitted by sexual contact, transfusion, and use of contaminated blood products and sharing contaminated needles [1].

During the last 20 years, HIV infection and severe HIV-related diseases (e.g., AIDS) have become a leading cause of illness and death in the United States. Approximately 800,000-900,000 persons in the United States are infected with HIV and approximately 275,000 of these persons might not know they are infected [2].

HIV-1 and HIV-2 viruses have been isolated from patients with AIDS and AIDS-related complex (ARC), high-risk persons for AIDS. HIV-1 and HIV-2 viruses delete T helper cells, a subpopulation of T cells for body defense, thus causing AIDS patients susceptible to opportunistic infections and developing malignant tumors. The incidence of specific antibodies to HIV-1 and HIV-2 is high in AIDS, ARC and persons with high risk for AIDS. The HIV-1 & HIV-2 Rapid Screen Test is designed to detect antibodies to HIV-1 and/or HIV-2 in AIDS patients, ARC or high risk persons and identify any potential donors carrying these antibodies in serum/plasma or whole blood specimens.

PRINCIPLE

Diagnostic Kit for Antibody to Human Immunodeficiency Virus (1+2) is a chromatographic immunoassay (CIA) for the detection of antibodies to HIV-1 and/or HIV-2 in human serum/plasma and whole blood. HIV-1 and HIV-2 specific recombinant antigens are separately precoated onto membrane in region 1 and 2 as a capture reagent on the test region. During the test, specimen is allowed to react with the colloidal gold particles, which have been labeled with HIV-1 and HIV-2 specific antigens. Antibodies to HIV-1 and/or HIV-2, if present, a red colored band will develop in region 1 and/or 2 on the membrane in proportion to the amount of HIV (1+2) antibodies present in the specimen. Absence of these red colored bands in the test region (region 1 and 2) suggests a negative result. To serve as a procedural control, red colored band in the control region will always appear regardless of the presence of antibodies to HIV-1/HIV-2.

REAGENTS AND MATERIALS PROVIDED

Each kit contains:

1. 40 Test Devices (individually pouched)
2. Each pouched contains one cassette with desiccant bags and a disposable plastic dropper.
3. One Dropper bottle of Diluent buffer (5 mL).
4. One operating instruction.

MATERIALS REQUIRED BUT NOT PROVIDED

1. Timer or stopwatch
2. Blood collection devices, for testing of venipuncture whole blood, serum or plasma
3. Biohazard disposal container
4. Disposable gloves

For Fingerstick samples the following additional material are required:

- Adhesive bandages
- Lancet capable of producing a 50 µl dropper
- Sterile wipes and sterile gauze pads

WARNING

For in vitro diagnostic use

Read the package insert completely before use. It is very important that the correct procedure is followed. Fail to add the patient sample may lead to a false negative result (i.e. a missed positive).

Read the package insert completely before using the product. The instructions must be followed carefully and avoid evaluating too many samples at one time.

PRECAUTIONS

Safety Precautions

1. All patient samples should be treated as if capable of transmitting diseases. (Dispose of used materials in a Bio-hazardous container)
2. Wear protective clothing such as laboratory coats, disposable gloves, and eye protection, when handling specimens.
3. Standard precautions for handling infectious agents should be observed when using this kit.
4. Wash hands thoroughly after use.

Appropriate biosafety practices should be followed when handling specimens and reagents. These precautions include, but are not limited to, the following:

1. Do not smoke, eat, drink, apply cosmetics or handle contact lenses in areas where specimens are handled.
2. Dispose of all specimens, used devices, and pipettes (or pipette tips) as though they are capable of transmitting infection. Disposable materials may be incinerated.
3. Use a separate disposable pipette (or pipette tip) for each specimen tested.
4. Do not pipette by mouth.

Handling Precautions

1. Do not use any device if the pouches have been perforated.
2. Each device is for single use only.
3. Do not mix reagents from different kit lots.
4. Do not use the kit past the expiration date (this date is printed on the box).
5. Adequate lighting is required to read the test results.
6. If Desiccant Packet is missing, DO NOT USE. Discard the test device, and a new test device should be used.
7. Dropper is provided to users who do not have pipette and other precision instruments. If users have pipettes with disposable pipette tips, they can accurately dispense 35 µl of sample in the sample well. Dispose of the pipette or the pipette tip once the sample has been delivered in to the sample well. Do not reuse droppers and pipette tips.

STORAGE

Diagnostic Kit for Antibody to Human Immunodeficiency Virus (1+2) (Colloidal Gold) should be stored at temperature ranges 4-30°C. Do not freeze. Foil pouch (inner packaging) is moisture resistant. Do not open the pouch until you are ready to perform a test. If the foil pouch is damaged then scrap it. When stored as indicated, test devices are stable until the expiration date marked on the pouch. Shelf-life of the sealed pouch is 24 months. Do not use beyond the indicated expiration date. Buffer should also be stored at 4-30°C in its original vial.

SAMPLE COLLECTION AND TEST PREPARATION

Fingerstick Specimens (Whole Blood)

1. Clean the area to be lanced with an alcohol swab.
2. Squeeze the end of the fingertip and pierce it with a sterile lancet.
3. Wipe away the first drop of blood with sterile gauze or cotton; collect the sample from the second drop.
4. Use micropipet to obtain about 2~3 drops (about 100 µl) fresh blood.

Plasma

1. Have a certified phlebotomist collect whole blood into a purple, blue or green top collection tube (containing EDTA, citrate or heparin, respectively) by veinpuncture.
2. Separate the plasma by centrifugation.
3. Carefully withdraw the plasma for testing, or label and store it at 2-8°C for up to two weeks. Plasma may be frozen at -20°C for up to one year. Avoid multiple freeze-thawing of samples.

Serum

1. Have a certified phlebotomist collect whole blood into a red top collection tube (containing no anticoagulants) by veinpuncture.
2. Allow the blood to clot.
3. Separate the serum by centrifugation.
4. Carefully withdraw the serum for testing, or label and store it at 2-8°C for up to two weeks. Serum may be frozen at -20°C for up to one year. Avoid multiple freeze-thawing of samples.

ASSAY PROCEDURE

Use one foil pouch per sample. First bring kits and samples to room temperature. Open the test pouch and place it on flat surface. Use it immediately.

Suck 1 drop (35 µl) sample with dropper in foil pouch. Add the sample in Sample Well. After the sample is completely absorbed, add 1 drop (35 µl) of diluent buffer. Observe the result between 5-15 minutes after the addition of the running buffer. Discard the test cassette after the 15 min reading.

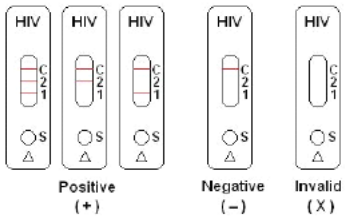
Note: the result of strong positive samples can show up in 5 min, while the result of weak positive samples may show up at 15 min.

Use a buffer bottle

Open the diluent buffer bottle to dispense by unscrewing the dome cap. Add 1 drop (35 µl) into the sample well. Screw back the dome cap immediately. Place it back in the kit box for storage as indicated in the instruction sheet.

Manufacture date and expire date of diluent buffer is indicated on the bottle label.

INTERPRETATION OF RESULTS



Note: 'C' – Control line; '1' -- HIV-1 Test line; '2' -- HIV-2 Test line

Negative: No apparent red band in the test region (1 and 2). Only one red band appears in the control region (C). This indicates that no HIV-1 or HIV-2 antibody has been detected.

Positive: In addition to the red band in the control region (C), other one or two red bands appear in the test region (1 and 2). This indicates that the specimen contains HIV-1 and/or HIV-2 antibodies.

Invalid: If no red band appears in the control region (C), regardless of the presence or absence of red lines in the test region (1 and 2).

It indicates a possible error in performing the test. The test should be repeated using a new device.

QUALITY CONTROL

An internal procedural control is immobilized in the test at control region. A red line will appear in the control region (C).

Built-In Control Features

Diagnostic Kit for Antibody to Human Immunodeficiency Virus (1+2) (Colloidal Gold) has a built in procedural control that demonstrates assay validity. A pink/red line appearing adjacent to the character 'C' indicates that the test runs correctly.

LIMITATION

1. The test is to be used for the qualitative detection of antibodies to HIV.
2. A negative result does not rule out infection by HIV because the antibodies to HIV may be absent or may not be present in sufficient quantity to be detected at early stage of infection.
3. A positive result, even a weak positive, must be verified with a confirmatory test (Western Blot or a certified ELISA test kit).
4. As with all diagnostic tests, the result must be correlated with clinical findings. If the test result is negative and suspicion still exists, additional follow-up testing using other clinical methods are recommended. Clinical correlation is indicated with appropriate counseling, medical evaluation and possibly additional testing to decide whether a diagnosis of HIV infection is accurate.
5. Diagnostic Kit for Antibody to Human Immunodeficiency Virus (1+2) (Colloidal Gold) is a screening rapid test. It cannot determine the subtype of HIV (HIV-1 or HIV-2). When both T1 and T2 show up, dilution study of the sample can be used for further sensitivity study. For further determination, please perform the test again with the 100-fold diluted sample with a new cassette.

PERFORMANCE CHARACTERISTICS

Clinical Study

A total of 27467 HIV samples were run on Diagnostic Kit for Antibody to Human Immunodeficiency Virus (1+2) (Colloidal Gold). The results are summarized in the Table 1 below.

Table 1 Results of Performance

Diagnostic Sample type	Number of sample tested	NewScen HIV(1+2) Diagnostic Kit	
		Negative	Positive
Positive	550	3(B)	547(A)
Negative	26917	26913(D)	4(C)

Sensitivity=A/(A+B)*100%=99.5% (95%CI: 98.4~99.9%)
Specificity=D/(C+D)*100%=99.9% (95%CI: 99.9~100%)
Total Accuracy=(A+D)/(A+B+C+D)*100%=99.9%

Reactivity with Seroconversion Panels

Six HIV-1 seroconversion panels were tested in comparison to licensed ELISA and Western Blot tests. Each panel consisted of sequential specimens obtained from a single individual during seroconversion. The six seroconversion panels consisted of 30 specimens. The results of this study are shown in Table 2.

Table 2 Summary of Seroconversion Panel Results

Panel	Relative Day of Bleed	ELISA	Western Blot	NewScen
PRB945	0	-	-	-
	3	-	-	-
	7	-	-	-
	13	-	-	-
	15	+	-	+
	20	+	+	+
PRB947	0	-	-	-
	9	+	/	+
	11	+	/	+
	20	+	+	+
PRB955	0	-	/	-
	3	-	/	-
	7	-	/	-
	12	+	/	+
	14	+	/	+
PRB956	0	-	-	-
	40	-	-	-
	42	-	-	-
	47	-	-	-
	50	-	-	-
PRB958	0	-	-	-
	2	-	-	-
	7	-	-	-
	9	-	-	-
	15	-	-	-
	17	-	-	-
PRB973	0	-	-	-
	2	-	-	-
	7	-	-	-
	11	+	/	+

Note: "-"Negative, "+"Positive, "/"Indeterminate

Reactivity with Low Titer Panel

A total of 16 specimens from Anti-HIV-1 Low Titer Performance Panel were tested. The results are shown in Table 3.

Table 3 Results Summary of HIV-1 Low Titer Panel

Panel	ELISA	Western Blot	NewScen
PRB109	+	/	+
	-	-	-
	-	/	-
	+	/	-
	-	-	-
	-	-	-
	+	/	+
	+	/	+
	+	+	+
	-	/	-
	+	/	+
	+	+	+
	+	/	+
	+	/	+
	+	+	+
	+	+	+

Note: "-"Negative, "+"Positive, "/"Indeterminate

Reactivity with HIV-2 Mixed Titer Panel

The sensitivity of Diagnostic Kit for Antibody to Human Immunodeficiency Virus (1+2) (Colloidal Gold) was evaluated by

testing Anti-HIV-2 Performance Panel PRF203. The panel consisted of 11 specimens. The results are shown in Table 4.

Table 4 Results Summary of HIV-2 Mixed Titer Panel

Panel	ELISA	Western Blot	NewScen
PRF203	+	+	+
	+	+	+
	+	/	+
	+	+	+
	+	+	+
	+	/	+
	+	+	+
	+	+	+
	+	+	+
	+	+	+
	-	-	-

Reactivity with HIV Worldwide Panel

WWRB305, an HIV Worldwide Performance Panel, was used to assess sensitivity of the Diagnostic Kit for Antibody to Human Immunodeficiency Virus (1+2) (Colloidal Gold) for HIV-1 specimens from various worldwide geographic regions. The panel consisted of 20 confirmed HIV antibody-positive specimens. The results are shown in Table 5.

Table 5 Results Summary of HIV Worldwide Panel

Panel	Country of Origin	Subtype	ELISA	Western Blot	NewScen
WWRB305	Kyrgyzstan	A	+	+	+
	Honduras	B	+	+	+
	Ecuador	B	+	+	+
	South Africa	C	+	+	+
	NA	C	+	+	+
	Germany	CRF01_AE	+	+	+
	Kyrgyzstan	CRF01_AE	+	+	+
	Nigeria	CRF02_AG	+	+	+
	Ecuador	CRF02_AG	+	+	+
	Kyrgyzstan	CRF02_AG	+	+	+
	Germany	CRF03_AB	+	+	+
	Kyrgyzstan	CRF03_AB	+	+	+
	Germany	D	+	+	+
	Germany	D	+	+	+
	Germany	G	+	+	+
	Ivory Coast	K	+	+	+
	Congo	H/A1	+	+	+
	Congo	K/CRF09	+	+	+
	Congo	G/CRF02	+	+	+
	Thailand	CRF01/CRF15	+	+	+

Possible Interferences from anticoagulants

Table 6 below shows the summary of results of Diagnostic Kit for Antibody to Human Immunodeficiency Virus (1+2) (Colloidal Gold) (three lots) with anticoagulants.

Table 6 Results from samples with anticoagulants

Product	No.	Heparin	EDTA	Citric Acid Sodium
Lot 1~3#	1	-	-	-
	2	-	-	-
	3	-	-	-
	4	-	-	-
	5	-	-	-
	6	-	-	-
	7	-	-	-
	8	-	-	-
	9	-	-	-
	10	-	-	-
	11	-	-	-
	12	-	-	-
	13	-	-	-
	14	-	-	-
	15	-	-	-
	16	-	-	-
	17	-	-	-
	18	-	-	-
	19	-	-	-
	20	-	-	-

Conclusion:

The results showed no interference from these substances.

To further evaluate the specificity of Diagnostic Kit for Antibody to Human Immunodeficiency Virus (1+2) (Colloidal Gold), the product was challenged with samples of different disease states. The tested interference include TB antibody, HBsAg, HBsAb, HCV antibody, TP antibody, RF, AFP, the third trimester of pregnancy serum, and HAV-IgM positive serum. The results are shown in Table 7.

Table 7 Results from samples with interferent

Sample Tested	Number Tested	Results of 3 lots		
		Lot 1#	Lot 2#	Lot 3#
TB antibody positive	20	-	-	-
HBsAg positive	20	-	-	-
HBsAb positive	20	-	-	-
HCV antibody positive	20	-	-	-
TP antibody positive	20	-	-	-
RF positive	20	-	-	-
Third trimester of pregnancy serum	20	-	-	-
AFP high levels serum	20	-	-	-
HAV-IgM positive serum	20	-	-	-
Bilirubin serum	20	-	-	-
Hyperlipemia serum	20	-	-	-
Hemolysis serum	20	-	-	-

Conclusion:

The above table showed that there was no interference by above disease state samples.

Precision

Intra-assay

In the study, 30 replicate assays were performed by 2 technologists with 3 positive and 2 negative specimens. Correct negative and positive results were registered in 100% of the assays.

Inter-assay

The study involved the same specimens (3 positive and 2 negative). The samples were analyzed by 2 technologists in different labs in

triplicate (total of 30). Independent assay data with Diagnostic Kit for Antibody to Human Immunodeficiency Virus (1+2) (Colloidal Gold) was originated from three different lots during 5-day testing. Again, expected negative and positive results were registered in 100% of the assays.

Stability:

Accelerated & Real-time stability data indicated that the product is stable for 2 years.

INDEX OF SYMBOLS

 Manufacture  Consult Instructions for Use

 For In-Vitro Diagnostic use only

 Lot number

 Stored at Room Temperature

Product disclaimer: This product has been manufactured under strict GMP regulation to ensure the diagnostic accuracy of the test. It is out of control of the manufacture when the test is performed in diverse environment and by diverse group of individuals that may affect the results to a certain degree.

Note: The manufacture, the distributor, or its associates will not be liable for any losses, claims, liability, costs or damages, whether direct or indirect or consequential arising out of or related to an incorrect diagnosis, whether a positive or negative by use of this product.

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