

Subject/Title: ASI EB VCA IgG EIA TEST		Doc#: 880096AG
Effective Date: 01/26/18	Supersedes Revision/Date: 02/18/16 (1)	Revision: 01/26/18 (2)
Prepared by: ASI	QA Approval by:	Copy/Dept.:

FOR IN VITRO DIAGNOSTIC USE**1.0 INTENDED USE:**

- 1.1 For the qualitative and semiquantitative detection of human IgG antibodies to Epstein-Barr (EB) viral capsid antigen (VCA) in human serum by enzyme immunoassay. The test may be used in conjunction with other serologicals, as an aid in the diagnosis of infectious mononucleosis.

2.0 SUMMARY AND EXPLANATION OF THE TEST:

- 2.1 Epstein-Barr virus (EBV) is the etiological agent of infectious mononucleosis (IM)¹. The designation of infectious mononucleosis classically refers to an Epstein-Barr virus-induced illness in young adults characterized by reactive blood smears, exudative pharyngitis, prominent cervical lymphadenopathy and serologically detectable heterophil antibodies. These clinical manifestations can also be caused by a number of other pathogenic agents including cytomegalovirus, Toxoplasma gondii, rubella virus, hepatitis virus, human immunodeficiency virus (HIV), and uncommonly by drugs such as Halothane, Hydantoin, Dapason and Azulfidine^{2,3,4}.
- 2.2 Diagnosis of acute EBV IM is generally confirmed by a positive heterophil antibody test. The severity of the disease however, is not indicated by the relative titer of heterophil antibodies (5). In addition, difficulties in diagnosis arise when the heterophil antibody test is negative, or when the clinical manifestations are atypical or unusually severe.
- 2.3 Heterophil-negative IM occurs in 10 to 20 percent of adults, and in an even greater percentage of children^{6,7}. IM diagnosis in these individuals may be confirmed by the detection and identification of antibodies to specific EB antigens which include: viral capsid antigen (VCA), early antigens diffuse and restricted (EA-D and EA-R), and Epstein-Barr nuclear antigen (EBNA).
- 2.4 IgG antibodies to VCA may be present early during EBV infection, but they persist indefinitely after the occurrence of clinical disease, and may merely indicate EBV infection at some time in the past. IgM antibodies to VCA on the other hand, are present in the circulation 1 to 6 weeks after the onset of EBV illness and usually disappear in 3 to 6 months. Thus the presence of VCA IgM usually suffices for the diagnosis of acute IM. Further verification may be obtained by testing for the presence of antibodies directed against the other EBV-specific antigens, early antigen and EBNA. Heterophil antibody negative sera demonstrating VCA IgM and transient levels of antibody to early antigen are considered diagnostic for acute IM. In contrast, antibodies to EBNA appear late during IM infections, and IgG antibodies to EBNA may persist for years, even for life, and are indicative of the convalescent phase of IM infection.
- 2.5 The EB VCA IgG EIA test is an ELISA test which utilizes a microwell format. Test results are obtained after one and one-half hours incubation time. They are objective and normalized as Index values, permitting uniformity of reporting.

3.0 PRINCIPLE OF THE PROCEDURE:

- 3.1 Diluted samples are incubated in VCA antigen-coated wells. VCA IgG antibodies (if present) are immobilized in the wells. Residual sample is eliminated by washing and draining, and conjugate (enzyme labeled antibodies to human IgG) is added and incubated. If IgG antibodies to VCA are present, the conjugate will be immobilized in the wells. Residual conjugate is eliminated by washing and draining, and the substrate is added and incubated. In the presence of the enzyme, the substrate is converted to a yellow end product which is read photometrically.

4.0 REAGENTS

Coated Wells	Coated with inactivated Epstein-Barr VCA antigen 12 eight-well strips.
Well Support	One.
Diluent*	25 ml (pink color). Phosphate-buffered saline with a protein stabilizer.
Calibrator 1*	0.3 ml. Human serum. Strongly reactive for VCA IgG antibodies.
Calibrator 2*	0.3 ml. Human serum. Moderately reactive for VCA IgG antibodies.
Positive Control*	0.3 ml. Human serum. Reactive for VCA IgG antibodies.
Negative Control*	0.3 ml. Human serum. Non-reactive for VCA IgG antibodies.
Conjugate	12 ml (green color). Goat anti-human IgG labeled with alkaline phosphatase (calf).
Substrate	12 ml. p-nitrophenyl phosphate.

Note: The substrate may develop a slight yellow color during storage. One hundred microliters of substrate should yield an absorbance value less than 0.35, when read in a microwell against air or water.

Wash Concentrate* 30 ml. Tris-buffered saline with Tween 20, pH 8.0. Prepare Wash Solution by adding the contents of the Wash Concentrate bottle to liter of distilled or deionized water.

Stop Reagent 12 ml. Trisodium Phosphate 0.5 M.

* Contains 0.1% sodium azide.

Store these reagents according to the instructions on the bottle labels. Do not allow them to contact the skin or eyes. If contact occurs, wash with copious amounts of water.

5.0 WARNINGS AND PRECAUTIONS

- 5.1 For in vitro diagnostic use.
- 5.2 Test samples, Calibrator(s), Controls and the materials that contact them, should be handled as potential biohazards. The calibrators and controls have been found to be negative for HIV, hepatitis B surface antigen and HCV antibodies by FDA

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licensed tests. However, because no method can offer complete assurance that HIV, hepatitis B virus, HCV or other infectious agents are absent, these materials should be handled at the Biosafety Level 2 as recommended for any potentially infectious serum or blood specimen in the Centers for Disease Control/National Institutes of Health Manual "Biosafety in Microbiological and Biomedical Laboratories", 1993, or latest edition.

- 5.3 The concentrations of anti-EB VCA IgG in a given specimen determined with assays from different manufacturers can vary due to differences in assay methods and reagent specificity.
- 5.4 Avoid contact with open skin.
- 5.5 Never pipet by mouth.
- 5.6 Certain of the test reagents contain sodium azide. Azides are reported to react with lead and copper in plumbing to form compounds that may detonate on percussion. When disposing of solutions containing sodium azide, flush drains with large volumes of water to minimize the build-up of metal-azide compounds.
- 5.7 R 21/22: Harmful in contact with skin and if swallowed.
- 5.8 S24/25 - 36/37/39: Avoid contact with skin and eyes. Wear suitable protective clothing, gloves and eye/face protection. For further information, refer to product SDS.
- 5.9 Do not interchange reagents from different reagent lots, except for Diluent, Wash Concentrate, Substrate and Stop Reagent.
- 5.10 Do not use reagents beyond their stated expiration date.
- 5.11 Incubation times recommended in the Test Procedure section should be adhered to.
- 5.12 Unused Coated Wells should be kept in their resealable bag with desiccant, and stored in the refrigerator.
- 5.13 Do not smoke, eat, drink, or apply cosmetics in areas where plasma/serum samples are handled.

6.0 HANDLING AND PROCEDURAL NOTES

- 6.1 In order to obtain reliable and consistent results, the instructions in the package insert must be strictly followed. Do not modify the handling and storage conditions for reagents or samples.
- 6.2 Do not use past the expiration date indicated on the kit.

7.0 STORAGE INSTRUCTIONS

- 7.1 Store all reagents at 2 to 8° C in an upright position when not in use. Do not freeze reagents.

8.0 INDICATIONS OF DETERIORATION

- 8.1 Turbidity or precipitation in controls is indicative of deterioration and the component should not be used.
- 8.2 Bacterial contamination of reagents or specimens may cause false positive results.

9.0 SPECIMEN COLLECTION AND STORAGE

- 9.1 Sera should be separated from clotted blood.
- 9.2 If specimens are not tested within 8 hours, they should be stored at 2 to 8° C. for up to 48 hours. Beyond 48 hours specimens should be stored at -20° C. or below.
- 9.3 Multiple freeze-thaw cycles should be avoided.
- 9.4 Samples containing visible particulate matter should be clarified by centrifugation; and hemolyzed, icteric, or grossly contaminated samples should not be used.
- 9.5 Samples should not be heat-inactivated before testing.

10.0 PERFORMANCE OF TEST

10.1 Materials Provided:

96 Tests	
Coated Wells	12 eight well strips
Well Support	1
Diluent	25 ml
Calibrator 1	0.3 ml
Calibrator 2	0.3 ml
Positive Control	0.3 ml
Negative Control	0.3 ml
Conjugate	12 ml
Substrate	12 ml
Wash Concentrate	30 ml
Stop Reagent	12 ml

10.2 Additional Materials Required

- 10.2.1 Microplate washer
- 10.2.2 Pipettors for dispensing 8, 100 and 200 µl
- 10.2.3 Timer
- 10.2.4 1 or 2 liter container for Wash Solution

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- 10.2.5 Distilled or deionized water
- 10.2.6 Dilution tubes or microwells
- 10.2.7 Microwell reader capable of reading absorbance at 405 nm. Dual wavelength readers are recommended.

11.0 TEST PROCEDURE

11.1 Preparation for the Assay

- 11.1.1 Allow all reagents and patient samples to reach room temperature before use. Return them promptly to refrigerator after use.
- 11.1.2 Prepare 1:51 dilutions of test samples, Calibrator(s), Positive and Negative Controls, in the test set Diluent. For example: add 4 µl of sample to 200 µl of Diluent in a dilution well or tube, and mix well.
Note: A single Calibrator (Calibrator 2) may be used; or Calibrator 1 and Calibrator 2 may be used to prepare a calibration curve.

12.0 ASSAY PROTOCOL

- 12.1 Place an appropriate number of Coated Wells in the Well Support.
Note: For combination testing (multiple assays per plate), the strips should be assembled on a white background with good lighting. Be sure to note the placement of each strip.
- 12.2 Transfer 100 µl of each diluted Calibrator, Control and patient sample to the wells.
Note: Include one well which contains 100 µl of Diluent only. This will serve as the reagent blank and will be ultimately used to zero the photometer before reading the test results, or it may be used as the zero point in a calibration curve.
- 12.3 Incubate the wells at room temperature (20 to 25° C.) for 30 ± 5 minutes.
- 12.4 Wash wells four times with at least 250 µL/well/wash. Do not allow the wells to soak between washes. Drain thoroughly after the last wash.
- 12.5 Place 2 drops (or 100 µl) of Conjugate into each well.
- 12.6 Incubate the wells at room temperature for 30 ± 5 minutes.
- 12.7 Wash wells four times with at least 250 µL/well/wash. Do not allow the wells to soak between washes. Drain thoroughly after the last wash.
- 12.8 Place 2 drops (or 100 µl) of Substrate into each well.
- 12.9 Incubate at room temperature for 30 ± 5 minutes.
- 12.10 Place 2 drops (or 100 µl) of Stop Reagent into each well.
- 12.11 Read and record the absorbance of the contents of each well at 405 nm against the reagent blank.
Note: Adjust the photometer to zero absorbance at 405 nm against the reagent blank. Readings should be made within 2 hours after the reactions have been stopped.

13.0 QUALITY CONTROL

- 13.1 The Calibrator(s), Positive, and Negative Controls must be included in each test run.
- 13.2 The absorbance value of Calibrator 1 must be at least 0.4 when read against the reagent blank.
- 13.3 The absorbance value of the reagent blank should be less than 0.35.
- 13.4 The Negative Control must have an Index value less than 0.9.
- 13.5 The Positive Control must have an Index value equal to, or greater than 1.1, when using a single Calibrator (Calibrator 2). When using the calibration curve, the Positive control must have an Index value within the range printed on the label. Users may supply an alternative Positive Control if they wish.
- 13.6 The Negative and Positive Controls are intended to monitor for substantial reagent failure. The Positive Control will not ensure precision at the assay cutoff. Additional controls may be tested according to guidelines or requirements of local, state and/or federal regulations or accrediting organizations.

14.0 INTERPRETATION OF RESULTS –

14.1 Calculation of Results

Test results may be calculated using a single calibrator (Calibrator 2), or using a calibration curve.

Single Calibrator (Calibrator 2)

Determine the Index value for each test sample (or Control) using the following formula:

$$\frac{\text{Calibrator Index}}{\text{Calibrator Absorbance}} \times \text{Test Sample Absorbance} = \text{Test Sample Index}$$

If the Calibrator is run in duplicate, use the average absorbance value to calculate results.

14.2 Calibration Curve

Alternatively, test results may be calculated from a three-point curve comprised of: Calibrator 1 (high-point), Calibrator 2 (mid-point) and the reagent blank (zero / origin), using a point-to-point curve fit.

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14.3 Interpretation of Results

Index Value	Interpretation
< 0.9	Negative for anti-EB VCA IgG antibody
≥ 1.1	Positive for anti-EB VCA IgG antibody
≥ 0.9 < 1.1	Equivocal*

14.3.1 *Index values which fall between 0.9 and 1.1 indicate an equivocal result. Subsequent samples should be drawn at least fourteen days later and tested simultaneously with the initial sample. If the subsequent sample is positive, seroconversion has occurred, which may be indicative of recent infection. If the subsequent sample remains equivocal, antibody status is undetermined and the sample is deemed equivocal. Other clinical and serological evidence should be sought in these cases.

14.3.2 The EB VCA IgG EIA cut-off values were based on statistical analyses, of the results of tests of 25 serum specimens which were negative for anti-VCA IgG antibodies when tested by another commercial VCA IgG test. The cutoff values were challenged in tests of positive and negative specimens (see Performance Characteristics).

14.3.3 Specimens which yield absorbance values above the range of the test set calibrator(s), may be pre-diluted in the test set Diluent and reassayed. The resulting Index value must be multiplied by the dilution factor. Example: If the specimen has been pre-diluted 1:5 before testing, the resulting Index value should be multiplied by 5.

14.4 Semiquantitative Interpretation:

Dose response experiments have been performed at Laboratory B (Miami, FL) by assaying serial dilutions of positive specimens. Typical results of these experiments are shown in Figure 1. An analysis of these experiments was performed to establish the criteria for recognizing significant changes in antibody levels. To determine significant differences between EB VCA IgG EIA Index values, calculate the ratio of the Index values, by dividing the larger Index value by the smaller one. If the ratio is ≤ 2.00, the difference is not significant. If the ratio is between 2.01 and 3.87, the difference is equivocal. If the ratio is ≥ 3.88, the difference is significant.

14.4.1 Values obtained with different manufacturer's assay methods may not be used interchangeably. The magnitude of the reported IgG level cannot be correlated to an endpoint titer. The magnitude of the assay result above the cut-off is not an indicator of the total antibody present.

15.0 LIMITATIONS OF THE PROCEDURE

- 15.1 The results obtained with the EB VCA IgG EIA test serve only as an aid to diagnosis and should not be interpreted as diagnostic in themselves. Test results should be evaluated in relation to patient symptoms, clinical history, and other laboratory findings.
- 15.2 The timing of the appearance of IgG antibodies to VCA is subject to variations among individuals and serological assays. Some sera drawn very early at the onset of symptoms, may not contain detectable levels of VCA antibody and may require the drawing of another test specimen 1-2 weeks later. Specimens collected too early during the course of the disease may not contain anti-EB VCA IgG antibody.
- 15.3 The assay's performance characteristics with immunosuppressed individuals have not been established.
- 15.4 The prevalence of IgG antibodies to VCA will affect the assay's predictive value.
- 15.5 This assay is not intended for viral isolation and/or identification.
- 15.6 The assays performance characteristics have not been established for testing newborn specimens, or cord blood, or matrices other than human serum.
- 15.7 Dose response experiments have demonstrated that specimens yielding EB VCA IgG EIA Index values up to 89.2 do not exhibit a high-dose hook effect.
- 15.8 The assays performance characteristics were not established for visual result determination.

16.0 EXPECTED VALUES

- 16.1 Nearly all individuals have been infected with EBV by the time they reach adulthood⁸. Characteristically, IgG antibodies to VCA appear relatively early during IM infections and persist for years, even for life.
- 16.2 Serum samples obtained randomly from 57 normal South Florida blood donors were assayed by the EB VCA IgG EIA test. All 57 samples tested positive for IgG antibodies to VCA. The samples yielded index values between 1.1 and 20.8, with a mean index value of 13.8.

Table 1. Results of EB VCA IgG EIA Tests of 57 Archival Specimens (frozen), from Normal South Florida Blood Donors. The Assays were Performed at Laboratory B (Miami, FL).

Index Value Ranges	Specimens	
< 1.1	0	0 %
≥ 1.1 to < 5	6	10.5 %
≥ 5 to < 15	20	35.1 %
≥ 15	31	54.4 %

17.0 PERFORMANCE CHARACTERISTICS

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17.1 Comparative Testing

The results of EB VCA IgG EIA tests correlate well with other commercial serological tests. Serum specimens obtained from normal South Florida blood donors, from patients whose sera were submitted to clinical laboratories in South Florida for diagnostic testing, and from serum brokers, were assayed by the EB VCA IgG EIA test, and other commercial serological assays. The assays were performed at an independent laboratory (Lab A, Miami, FL), and at Laboratory B (Miami, FL). Forty-eight percent of the serum specimens tested at Laboratory A were from female donors ranging in age from 1 to 89 years (mean = 24 years). Fifty-two percent were from male donors between 1 and 75 years of age (mean = 28 years). The results obtained in these studies are shown below in tables 2 and 3, respectively.

Table 2. Results of Tests of 90 Archival Patient Specimens Tested at Laboratory A (Miami, FL) Using the EB VCA IgG EIA Test and Another Commercial Test

Comparative EB VCA IgG EIA						
Test #1	Positive	Equivocal	Negative		%	95%CI**
Positive	74	2	0	Relative sensitivity*	100	96.0 to 100
Equivocal	0	0	0			
Negative	7	4	3	Relative specificity*	30	1.6 to 58.4
				Overall Agreement*	91.7	85.8 to 97.6

* Excluding equivocal results
** Calculated by the Normal Method⁷.

Table 3. Results of Tests of 157 Archival Patient Specimens Tested at Laboratory B (Miami, FL) Using the EB VCA IgG EIA Test and Another Commercial Test.

Comparative EB VCA IgG EIA						
Test #2	Positive	Equivocal	Negative		%	95%CI**
Positive	130	2	11	Relative sensitivity*	92.2	87.8 to 96.6
Equivocal	2	1	0			
Negative	1	1	9	Relative specificity*	90.0	71.4 to 100
				Overall Agreement*	92.1	87.7 to 96.4

* Excluding equivocal results
** Calculated by the Normal Method⁷.

Please be advised that "relative" refers to the comparison of this assay's results to that of a similar assay. There was not an attempt to correlate the assay's results to disease presence or absence. No judgement can be made on the comparison assay's accuracy to predict disease.

17.2 Sensitivity and specificity relative to serological profile

One hundred and fifty-seven archival serum specimens (see table 3) were tested at Laboratory B using the EB VCA IgG EIA test, and other commercially available EIA tests for detecting VCA IgG, VCA IgM and EBNA IgG. One hundred and thirty-seven of these sera were able to be characterized as acute (VCA IgM antibody present and EBNA IgG antibody absent), seropositive (VCA IgG and EBNA IgG antibodies present and VCA IgM antibodies absent) or seronegative (no serological evidence of EBV IgM, EBV IgG or EBNA IgG antibodies), on the basis of their serological profile. The sensitivity, specificity and agreement of the EB VCA IgG EIA assay were determined based on these characterizations. It was assumed that the VCA IgG response should be negative for seronegative samples, and positive for the acute and convalescent samples. The results have been summarized below in table 4.

Table 4. Results of Tests Performed at Laboratory B, with 137 Selected Serum Specimens, Using the EB VCA IgG EIA Test, and Other Commercially Available Tests for VCA IgG, VCA IgM and EBNA IgG Antibodies.

EB VCA IgG EIA	Serum Characterization		
	Acute VCA IgM+ EBNA IgG-	Seropositive VCA IgM- VCA IgG+ EBNA IgG+	Seronegative VCA IgM- VCA IgG- EBNA IgG-
Positive	21	100	0
Negative	3	2	9
Equivocal	1	0	1
Total	25	102	10

Relative sensitivity (Acute) = 21/24 = 87.5 %, 95 % CI = 74.3 % to 100 %
 Relative sensitivity (Seropositive) = 100/102 = 98.0 %, 95 % CI = 95.3 % to 100 %
 Relative specificity (Seronegative) = 9/9 = 100 %, 95 % CI = 92.0 % to 100 %
 Relative agreement = 130/135 = 96.3 %, 95 % CI = 93.1 % to 99.5 %

Equivocal results were not included in the calculations, nor were they retested.

95 % confidence intervals (CI) were calculated using the normal method.

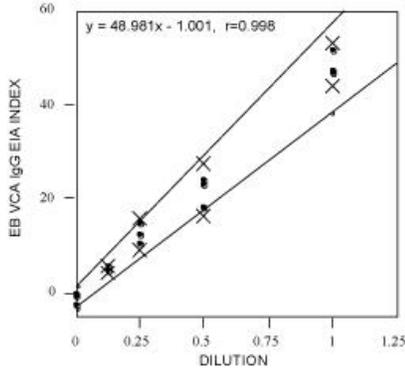
The seronegative 95% confidence interval was calculated assuming 0.1 false positive.

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17.3 Titration Curve

Several strongly positive serum specimens were serially diluted (two-fold) in triplicate in the test kit Diluent, and assayed by the EB VCA IgG EIA test. Typical results are shown in Figure 1.

Figure 1. Titration Curve for a Strongly Positive Specimen.



The triplicate data for each dilution are shown as points, the 95% confidence limits for each set of triplicate data are indicated by (x's), and the 95% confidence limits for the slopes and y-intercepts are represented by straight lines. The formula for the linear regression for the triplicate data is also shown in Figure 1.

17.4 Cross-reactivity study

The EB VCA IgG EIA test does not cross-react with antibodies directed against other Epstein-Barr virus antigens, other herpes viruses, and other unrelated viruses. Of ten specimens which were unreactive in the EB VCA IgG EIA test, 2 were positive for VCA IgM antibody, 3 EB NA antibody, 2 herpes simplex virus antibody, 3 cytomegalovirus antibody, 3 varicella zoster virus antibody, 4 rubella antibody and 2 measles antibody.

17.5 Precision

Eight serum specimens (2 negative and 6 positive) and the EB VCA IgG EIA Positive and Negative Controls, were assayed in triplicate, on three separate occasions.

The precision experiments were performed manually at an independent laboratory (Lab A), and at Laboratory B. These results are shown below in tables 5 and 6, respectively.

Table 5. Results Intra-assay and Interassay Precision Tests Performed at Lab A. Values were calculated from EB VCA IgG EIA Index Values.

SAMPLE	INTRA-ASSAY			INTERASSAY		
	INDEX			INDEX		
	MEAN	S.D.	C.V. %	MEAN	S.D.	C.V. %
Pos. Control	2.6	0.115	2.6	4.2	0.316	7.6
Neg. Control	0.8	0.058	NA	0.8	0.000	NA
1	0.3	0.000	NA	0.3	0.067	NA
2	0.3	0.058	NA	0.3	0.000	NA
3	7.1	0.874	12.2	6.8	0.719	10.6
4	5.4	0.115	2.2	5.4	0.497	9.2
5	3.0	0.115	3.9	2.9	0.141	4.9
6	3.6	0.306	8.4	3.6	0.265	7.4
7	4.2	0.350	8.3	4.3	0.330	7.8
8	4.0	0.250	6.3	3.7	0.360	9.8

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Table 6. Results Intra-assay and Interassay Precision Tests Performed at Lab B. Values were calculated from EB VCA IgG EIA Index Values.

SAMPLE	INTRA-ASSAY			INTERASSAY		
	MEAN	S.D.	C.V. %	MEAN	S.D.	C.V. %
Pos. Control	9.1	0.231	9.1	2.4	0.207	8.5
Neg. Control	0.3	0.058	NA	0.2	0.000	NA
1	0.3	0.000	NA	0.3	0.053	NA
2	0.2	0.000	NA	0.2	0.033	NA
3	6.7	0.321	4.8	6.4	0.381	6.0
4	6.9	0.400	5.8	6.5	0.451	6.9
5	3.3	0.577	17.3	2.9	0.468	16.3
6	4.4	0.361	8.2	4.0	0.438	10.9
7	6.6	0.400	6.2	5.8	0.620	10.7
8	4.4	0.100	2.3	4.1	0.490	12.0

18.0 REFERENCES

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19.0 TECHNICAL INFORMATION: (801) 489-8911 or (800) 654-0146

	Manufactured for: Arlington Scientific, Inc. 1840 N Technology Drive, Springville, UT 84663 (USA)		JB Morphet Ltd. 34 Ashdale Road Kesgrave Suffolk IP5 2PA United Kingdom
	Lot No.		Expiration Date
	96 Tests		Catalog No.
	In vitro diagnostic use only		Temperature Limitations