SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. General Information

Device Generic Name
Enzyme Linked Immunosorbent Assay, Parvovirus B19 IgG

Device Trade Name
Biotrin Parvovirus B19 IgG Enzyme Immunoassay

Classification Name
Not classified

Submitted By

Hogan and Hartson L.L.P.
555 Thirteenth Street, NW
Washington, DC 20004

on behalf of:

Biotrin International, Limited
93 The Rise
Mount Merrion,
Co. Dublin,
Ireland

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August 6, 1999

II. Indication for Use

Intended Use

The Biotrin Parvovirus B19 IgG Enzyme Immunoassay is intended for the qualitative detection of IgG antibodies to B19 virus (B19V, previously known as human parvovirus B19) in human serum, lithium heparin, EDTA, and citrated plasma. This test, in conjunction with the Biotrin Parvovirus B19 IgM Enzyme Immunoassay, may be used for testing women of childbearing age to determine their serological status where there is a suspicion of exposure with B19V. The results of these assays may be used to make a serological determination of past, recent, or current infection with B19V. The clinician should consider the results of these assays as presumptive for risk of fetal infection with B19V. The test may also be used for all patients as an aid in the diagnosis of fifth disease (erythema infectiosum).

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Background

B19V (previously known as human parvovirus B19) is a member of the family *Parvovirinae*, genus *Erythrovirus*.[1] The virus is an iscosahedral, non-enveloped virus of 18-25nm diameter and comprises a linear single stranded DNA genome (5.5kb) which is encapsulated within an outer capsid.[2] The viral capsid is composed of two structural proteins, namely VP1 (83kDa) and VP2 (53kDa).

B19V was first identified as a human pathogen in 1975 and has subsequently been shown to be the causative agent of a number of clinical conditions.[3, 4, 5] The spectrum of symptoms caused by B19V, including rash, arthralgia and transient aplastic crisis are generally self-limiting in healthy individuals. Serious complications due to infection may arise in certain populations including immunocompromised patients and pregnant women. With pregnant women, infection during pregnancy may lead to fetal death.[6] In the majority of pregnancies when B19V infection occurs a normal delivery at term results. Fetal death is thought to occur in less than or equal to 12% of cases.[7, 8] B19V infection during pregnancy has also been shown to cause non-immune fetal hydrops. It has been reported that between 4.2 and 16% of fetal hydrops cases may be due to B19V infection.[9, 10] It is thought that severe fetal anemia, where hemoglobin levels fall to less than 2g/dl, is the primary cause of fetal hydrops.[11]

In vivo, B19V replication has been shown to occur primarily in the erythroid progenitor cells. The cellular receptor for the virus has been identified as the P antigen of the blood group P system.[12] The authors also demonstrated *in vitro* that the addition of excess P antigen or antibody [anti-P antigen], could confer protection to erythroid progenitor cells against B19V infection. These observations were confirmed recently when it was demonstrated that individuals lacking the P antigen were resistant to B19V infection.[13] Cryo-electron microscopy analysis of VP2 capsids alone and complexed to the P antigen have further elucidated the mechanism of B19V infectivity.[14] These authors demonstrated that a tetrasaccharide component of the P antigen comfortably fits into a structure on the surface of the B19V VP2 protein. This provides a molecular mechanism for the cellular tropism of B19V.

It is now apparent that the immune response against B19V is unique. Antibodies (IgG) raised against linear epitopes on the VP1 and VP2 protein are lost after about 1-year post-infection whereas those directed against VP1 and VP2 conformational epitopes are maintained.[15, 16, 17] The recombinant baculovirus-expressed VP2 antigen used in the Biotrin Parvovirus B19 IgG enzyme immunoassay is isolated from *Spodoptera frugiperda* insect cells using non-denaturing conditions. This process maintains the integrity of conformational epitopes and minimizing the risk of false negativity due to the absence of relevant epitopes.

Exposure of healthy seronegative individuals to B19V results in a typical immune response whereby IgM levels rise soon after infection followed very shortly by production of anti-viral IgG with concomitant reduction in serum IgM levels.[4] Elevations in antibody (IgG) titer have been detected in seropositive individuals when re-exposed to B19V.[4, 18] Immunocompromised individuals may not develop this conventional antibody response and so are more likely to develop chronic viremia.[2]

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III. Device Description

A. Device Components

Biotrin International, Limited, furnishes the device as a kit containing the following components:

Coated ELISA Plate - 12 x 8 microwells coated with purified recombinant VP2 protein.

Calibrator - human sera containing anti-B19V IgG in a stabilizing buffer with thimerosal (0.01%).

Low Positive Control - weakly reactive human sera containing anti-B19V IgG in a stabilizing buffer with thimerosal (0.01%).

Negative Control – nonreactive human sera in a stabilizing buffer with thimerosal (0.01%).

Enzyme Conjugate - rabbit anti-human IgG horseradish peroxidase conjugate in a stabilizing buffer with thimerosal (0.01%).

Sample Diluent Concentrate - concentrated PBS buffer (21x) containing surfactant and thimerosal (0.01%).

Wash Concentrate - concentrated PBS buffer (20x) containing surfactant and thimerosal (0.01%).

Substrate - tetramethylbenzidene (TMB) solution.

Stop Solution - 1N H_2SO_4.

B. Device Operations:

The Biotrin Parvovirus B19 IgG Enzyme Immunoassay uses a microwell format. The test is a sandwich enzyme immunoassay for the detection of IgG class antibodies to B19V in human serum or plasma. If present, specific anti-B19V IgG will bind to the wells coated with B19V recombinant VP2 protein. Following a wash step, peroxidase-labeled rabbit anti-human IgG is added which binds to the human anti-B19V IgG present. The whole complex is then detected by addition of tetramethylbenzidine substrate that turns blue in the presence of peroxidase. A stable yellow product is achieved by the addition of a stopping reagent.

IV. Contraindications, Warnings and Precautions

There are no known contraindications for the Biotrin Parvovirus B19 IgG Enzyme Immunoassay.

See labeling for warnings and precautions.

V. Alternative Practices and Procedures

The usual clinical symptoms of B19V infection are rash (erythema infectiousum), arthralgia, malaise and mild fever. Partial diagnosis of viral infection can be made based on these symptoms. In the case of *in utero* infection, ultrasound is used to evaluate the status of the fetus if B19V infection is suspected. Alternative *in vitro* diagnostic techniques that are used to detect the presence of anti-B19V IgG include immunofluorescence and immunoblot analysis of patient sera.

There are no FDA approved methods for the detection of anti-B19V IgG by immunofluorescence or Western blot.

VI. Marketing History

The Biotrin Parvovirus B19 IgG Enzyme Immunoassay has been marketed since 1992 outside the U.S. and is currently marketed in Canada, Australia, South Africa and in the following European countries: The United Kingdom, Germany, France, The Netherlands, Belgium, Italy, Sweden, Norway, Denmark, Portugal, Spain and Ireland.

No product recalls or withdrawals have occurred for any reason related to the safety and effectiveness of the device.

VII. Adverse Effects of the Device on Health

The precise level of anti-B19V IgG that confers immunity has yet to be established. Although unlikely, the detection of anti-B19V IgG may not mean the individual is immune from reinfection with B19V.

False positivity

The true detection of anti-B19V IgG is indicative of past infection with B19V. Any sample which incorrectly tests positive for anti-B19V IgG due to cross-reactivity with the VP2 antigen is termed a false positive. The false detection of anti- B19V IgG in these samples can lead to the incorrect diagnosis that a previous B19V infection has occurred and that the individual may be immune to future B19V infection. In clinical terms, a false diagnosis of past B19V infection may prevent the initiation of therapy such as passive immunization with serum containing B19V IgG designed to prevent viral replication and disease symptoms and consequences. Misdiagnosis may lead to the patient not receiving the necessary treatment to prevent viral infection. If this false positivity occurs with a pregnant woman, she and her physician will have a false sense of security that she is protected from infection with B19V.

False negativity

False negativity in the Biotrin Parvovirus B19 IgG Enzyme Immunoassay may mean that a past infection would go undetected. If there is a suspicion of a past B19V infection, then any sample giving an unexpectedly negative result for IgG seropositivity should be retested at a later date (2-3 weeks later) to recheck the B19V IgG status of the individual. Analysis of previous samples for IgM/G status would also be advisable in such cases to check for any evidence of IgM seroconversion or previous IgG positivity. False negativity may also occur if

the patient is immunocompromised and general immunoglobulin production is suppressed. Results obtained from immunocompromised individuals must be carefully interpreted. Patient history and clinical symptoms must be fully evaluated to ensure that a misdiagnosis of recent or past B19V based on false negativity does not occur.

VIII. Summary of Studies

A. Summary of Non-Clinical Studies

Clinical Specimen Type

The following specimen types have been found compatible with the Biotrin Parvovirus B19 IgG Enzyme Immunoassay:

1. Serum
2. EDTA plasma
3. Heparinized plasma
4. Citrated plasma

Product Stability (Transport and Storage)

Three master lots of Biotrin Parvovirus B19 IgG Enzyme Immunoassay were stored at 2-8 °C to determine the optimum storage for product stability. Stability studies support product storage at 2-8 °C for up to 13 months.

Immunoglobulin Class Specificity

Class specificity of the device was evaluated by testing both high positive anti-B19V IgG and IgM containing sera in the Biotrin Parvovirus B19 IgG Enzyme Immunoassay with and without IgG and IgM absorbents, respectively.

Ten B19V IgG positive sera were tested:

Without Adsorbents: As a control to demonstrate the high positive B19V IgG status of the sera.

IgM adsorbed: To show that IgM removal does not significantly affect the absorbance values relative to the control and therefore confirm IgM is not contributing to the signal.

IgG adsorbed: To show that IgG removal virtually eliminates the signal demonstrating absorbent efficacy.

Ten B19V IgM positive sera were tested on the Biotrin Parvovirus B19 IgG Enzyme Immunoassay:

Without adsorbent: To show that the Biotrin Parvovirus B19 IgG Enzyme Immunoassay does not detect IgM.

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IgM adsorbed: To show that the absorbance values are not significantly different between the absorbed and the unabsorbed IgM positive sera.

IgG adsorbed: To show that IgG removal has no significant effect on the absorbance values between the absorbed and the unabsorbed B19V IgM positive sera.

It was concluded that the Biotrin Parvovirus B19 IgG Enzyme Immunoassay only detects B19V IgG and not B19V IgM. Adsorbtion of IgM does not affect the Biotrin Parvovirus B19 IgG Enzyme Immunoassay result and adsorbtion of IgG produces the expected negative result confirming the class specificity of the device.

Intra-assay Reproducibility:

A series of specimens, ranging in B19V IgG levels from weakly to strongly reactive, were each assayed a total of twenty two times. Replicates were tested on a single ELISA plate from a single master lot of product. The resultant optical density (OD) values were summated and the mean OD value (Table 1).

Table 1: Intra-assay reproducibility.

Test Specimen	Mean OD	SD	%CV	n
SR-A•	1.590	0.012	0.8	22
SR-B•	1.261	0.025	2.0	22
SR-C*	1.853	0.045	2.4	22
SR-D**	1.862	0.050	2.7	22
SR-E***	1.837	0.031	1.7	22
WR-A•	0.380	0.012	3.2	22
WR-B•	0.310	0.010	3.2	22
WR-C*	1.305	0.034	2.6	22
WR-D**	1.183	0.019	1.6	22
WR-E***	1.104	0.018	1.6	22
UR-A•	0.190	0.010	5.3	22
UR-B•	0.070	0.006	8.6	22
UR-C*	0.062	0.005	8.1	22
UR-D**	0.068	0.007	10.3	22
UR-E***	0.058	0.004	6.9	22

SR: strong reactive, WR: weak reactive, UR: unreactive, • Serum, * EDTA plasma, **Heparinized plasma, ***Citrated plasma.

Standard deviation and percentage coefficient of variation (% CV) in terms of assay index value, for the above specimens, are given in Table 2.

Table 2: Intra-assay reproducibility expressed in terms of Index values.

Test Specimen	Mean Index	SD	%CV	n
SR-A•	5.560	0.120	2.2	22
SR-B•	4.510	0.091	2.0	22
SR-C*	6.464	0.156	2.4	22
SR-D**	6.497	0.176	2.7	22
SR-E***	6.408	0.110	1.7	22
WR-A•	1.280	0.040	3.1	22
WR-B•	0.950	0.040	4.2	22
WR-C*	4.467	0.117	2.6	22
WR-D**	4.049	0.064	1.6	22
WR-E***	3.781	0.061	1.6	22
UR-A•	0.580	0.020	3.5	22
UR-B•	0.220	0.017	7.7	22
UR-C*	0.194	0.015	7.7	22
UR-D**	0.214	0.023	10.8	22
UR-E***	0.180	0.013	7.2	22

SR: strong reactive, WR: weak reactive, UR: unreactive, • Serum, * EDTA plasma, **Heparinised plasma, ***Citrated plasma.

Inter-laboratory Reproducibility

Inter-laboratory reproducibility was investigated at two independent laboratories and at Biotrin International. Each site evaluated three master lots of the Biotrin Parvovirus B19 IgG Enzyme Immunoassay against a defined panel of coded specimens comprising strongly reactive (serum n=3, heparinized plasma n=1, and EDTA plasma n=1), weakly reactive (serum n=5, heparinized plasma n=1, EDTA plasma n=1) and unreactive (serum n=2, heparinized plasma n=1, EDTA plasma n=1) specimens. Inter-laboratory reproducibility data are presented below (Table 3). For each master lot, each sample was assayed three times per day (in duplicate), on three different days, at each laboratory site. Each sample was assayed 81 times, except for one strongly reactive specimen, which was assayed 72 times, and one weakly reactive specimen that was assayed 80 times. Linear regression analysis of inter-laboratory reproducibility demonstrated correlation between results, analysed in terms of OD and index values, at all test sites and across all master lots (y = 0.969 x = -0.112 R^2= 0.993, y= 1.068 x= 0.065 R^2 = 0.990, and y = 0.958 x= 0.073 R^2= 0.990 for site 1 versus 2, site 2 versus 3 and 1 versus 3, respectively).

Table 3: Overall detection rate for the Biotrin Parvovirus B19 IgG Enzyme Immunoassay.

No. of Specimens	Specimen Type	Detection rate (Expected result/Total number of times assayed)
5	Strongly reactive	100% (396/396)
7	Weakly reactive	99.8% (565/566)
4	Unreactive	100% (324/324)

When these data are analysed in terms of inter-assay reproducibility, the Biotrin Parvovirus B19 IgG Enzyme Immunoassay demonstrates good correlation in test results between different laboratories and different master lots. Reproducibility data for six test specimens are given in Tables 4 and 5.

Table 4: Overall interassay reproducibility. Data (OD) accumulated from 3 test sites and 3 Master lots of Biotrin Parvovirus B19 IgG Enzyme Immunoassay.

Specimen	Mean OD	SD	%CV	n
PC	1.971	0.218	11.1	81
NC	0.034	0.018	52.9	81
LPC	0.509	0.092	18.1	81
SR1*	1.445	0.225	15.6	81
SR2**	1.362	0.251	18.4	81
SR3•	1.104	0.201	18.2	81
SR***	1.373	0.117	8.5	9
WR1•	0.537	0.108	20.1	81
WR2•	0.518	0.085	16.4	81
WR3•	0.466	0.110	23.6	81
UR***	0.044	0.005	11.4	9

PC: assay calibrator, NC: assay negative control, LPC: assay low positive control, SR: strong reactive, WR: weak reactive, UR: unreactive. • Serum, * EDTA plasma, **Heparinized plasma and ***Citrated plasma (studies conducted at Biotrin only).

Table 5: Overall interassay reproducibility. Data (Index Values) accumulated from 3 test sites/3 Master lots of Biotrin Parvovirus B19 IgG Enzyme Immunoassay.

Specimen	Index	SD	%CV	n
NC	0.209	0.020	9.6	9
LPC	1.413	0.101	7.2	9
SR1*	5.081	0.583	11.5	81
SR2**	4.778	0.610	12.8	81
SR3•	3.872	0.487	12.6	81
SR4***	4.423	0.262	5.9	9
WR1•	1.883	0.293	15.6	81
WR2•	1.814	0.264	14.6	81
WR3•	1.550	0.234	15.1	81
UR***	0.141	0.015	10.6	9

NC: assay negative control, LPC: assay low positive control, SR: strong reactive, WR: weak reactive. • Serum, * EDTA plasma, **Heparinized plasma and ***Citrated plasma (studies conducted at Biotrin only).

WHO International Standard

The Biotrin Parvovirus B19 IgG Enzyme Immunoassay has been calibrated to the World Health Organization (WHO) Parvovirus B19 IgG International Standard (IS). The Biotrin Parvovirus B19 IgG Enzyme Immunoassay cut-off value equates to an IS level of 3-5 IU/mL. No claims for immunoassay quantitation should be implied from this statement, it is solely intended to indicate that the Biotrin Parvovirus B19 IgG Enzyme Immunoassay is compatible with the WHO International Standard.

Center for Disease Control and Prevention B19V Serology Panel

Testing of the Center for Disease Control and Prevention (CDC) B19V Serology Panel was performed by Biotrin. This is a 100-member sera panel that has been characterized by patient clinical presentation, serology testing with native antigen enzyme immunoassays for IgG and IgM, and some B19V polymerase chain reaction testing. Testing of this panel with the Biotrin Parvovirus B19 IgM Enzyme Immunoassay was performed at CDC.

The panel consists of 73% positive and 27% negative anti-B19V IgG samples. The Biotrin Parvovirus B19 IgG Enzyme Immunoassay demonstrated 99.0% total agreement with the CDC results (one specimen did not have sufficient quantity for Biotrin testing). Of the results obtained by Biotrin International, Limited, there was 98.6% agreement with the positive specimens and 100% agreement with the negative specimens.

Cross-Reactivity

The majority of people have been exposed to B19V upon reaching adulthood, hence a relatively high IgG seroprevalence rate is observed in the adult population.[19] Therefore, it would be expected that samples containing potentially cross-reactive

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antibodies would yield the same level of positivity (approximately 70%) as an apparent healthy group. A total of 25 sera, all testing IgG positive for variety of conditions (Table 6), were included in this study. All samples were tested on the Biotrin Parvovirus B19 IgG Enzyme Immunoassay.

Table 6: Overall Summary of the Biotrin Parvovirus B19 IgG Enzyme Immunoassay specificity results.

Clinical Diagnosis (IgG+)	Total Number	Number Positive	Number Negative	Number Equivocal	% Positive
Rubella	5	5	0	0	100
Varicella	5	3	2	0	60
Mumps	5	2	3	0	40
Herpes I, II	5	5	0	0	100
Rubeola	5	3	2	0	60
CMV	5	4	1	0	80
EBV	5	5	0	0	100
Lyme disease	5	4	1	0	80
Toxoplasmosis	5	5	0	0	100
Overall Numbers	45	36	9	0	
Overall %		80	20	0	80

The overall rate of positivity observed is 80%, which is in line with published literature.[20]

Clinical Studies

Seroprevalence

A total of 399 samples from two separate US healthy blood donor populations (age range: 17-75) were tested using the Biotrin Parvovirus B19 IgG Enzyme Immunoassay. The total seroprevalence was 73.2%. Anti-B19V IgG positivity was essentially unaffected by sex and the geographical location from which the samples were derived. The only factor that appears to affect the rate of positivity is age. This is in agreement with previous studies relating to seroprevalence and age.[19]

Clinical Trial

A study was conducted at the Magee Womens Hospital, Pittsburgh, PA, using archival serum specimens. The principal investigator was Jeanne A. Jordan, Ph.D. The study population was pregnant women who had specimens submitted for B19V serology testing. The majority of the specimens were collected from women who had exposure to individuals infected or suspected of being infected with B19V. Single point specimens were available from 239 individuals. Ages of women in this study ranged from 15 to 43 years. With a median of 32 and an average of 31 years.

In addition to the Biotrin Parvovirus B19 IgG Enzyme Immunoassay, the specimens were tested for the presence of anti-B19V IgG antibodies by several reference methods. These methods included immunofluorescence (IgG and IgM), Western blot (IgM), and immunoblot (IgG). Characterization studies for the reference methods were submitted as part of the Premarket Approval Application.

Since B19V cannot be easily isolated using cell culture, and the infection's clinical presentation may be confused with other viral exanthemas, the study data were evaluated based on serological diagnosis. Based on the reference assay results, the specimens were divided into three categories "previously infected," "acute/recent infection," and "not previously infected."

For an individual to be considered "previously infected" anti-B19V IgG had to be detected by at least one reference method and no anti-B19V IgM could be detected.

For an individual to be considered as "acute/recent infection" anti-B19V IgM had to be detected by at least one reference method. Confirmation of this serological diagnosis was the finding of anti-B19V IgG in the same or a subsequent specimen. Since anti-B19V IgG is usually detected at the same time as anti-B19V IgM, the finding of anti-B19V IgG helps validate the anti-B19V IgM result. Therefore, a specimen was scored as an "acute/recent infection" if both anti-B19V IgG and IgM were detected. If only anti-B19V IgM were detected, it was considered a tentative serological diagnosis.

The serological diagnosis of "not previously infected" was not finding either anti-parvovirus IgG or IgM by any of the reference methods.

The above method for interpreting serological results for B19V infection has been published.[7]

The following table shows the serological diagnostic criteria for specimen result and the number of specimens found for each reference method result permutation:

IFA IgG	IFA IgM	IB IgG	WB IgM	No. Pts.	Patient's Serological Status
+	-/E*	+	-	141	Previously infected
-/E	-	+	-	6	
+	+	+	+	13	Acute/Recent Infection
+	+	+	-	3	
+	-	+	+	2	
-	+	+	+	1	
-	-	-	-	73	Not previously infected
			Total =	239	

*E = equivocal
Note: Other diagnostic permutations = 0, not shown.

The number of "previously infected" individuals (147/239, 61.5%) correlates well with other anti-B19V IgG epidemiological studies.

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The following table shows the results when the Biotrin Parvovirus B19 IgG and IgM Enzyme Immunoassays' results were compared to the reference methods serological diagnosis. The same result criteria were applied to the Biotrin assays as to the reference methods.

Serological Diagnosis		Acute/Recent Infection IgG+/IgM+ IgG-/IgM+ (n=19)	Previously Infected IgG+/IgM- (n=147)	Not Previously Infected IgG-/IgM- (n=73)
Biotrin Parvovirus B19 EIAs	Agree	15	143	73
	Disagree	4#	4*	0
	Agreement	78.9% (15/19)	97.3% (143/147)	100% (73/73)
	95% CI	54.9 to 94.0	93.2 to 99.2	95.1 to 100

Note: #4 specimens were Biotrin Parvovirus B19 Enzyme Immunoassay IgG+/IgM-
*1 specimen was Biotrin Parvovirus B19 Enzyme Immunoassay IgG+/IgM+ and 3 were Biotrin Parvovirus B19 Enzyme Immunoassay IgG-/IgM- (1 specimen was IB IgG VP1+)

There were no specimens for the "acute/recent infection" group where the Biotrin Parvovirus B19 IgG Enzyme Immunoassay was nonreactive when the Biotrin Parvovirus B19 IgM Enzyme Immunoassay was reactive. From the above information, it is assumed that the most efficient use of the Biotrin Parvovirus B19 Enzyme Immunoassays will be when they are used in conjunction. A reactive anti-B19V IgG will validate the reactive anti-B19V IgM result. If anti-B19V IgG is not detected, a new specimen should be drawn and reanalyzed for anti-B19V IgM.

The above results show that four specimens from the reference method "acute/recent infection" group were categorized as "previously infected" by the Biotrin assays. One specimen from the reference method "previously infected" group was categorized as an "acute/recent infection." Three specimens from this group were categorized as "not previously infected." In the following tables the false negative results incorporate appropriate misses from the other serological diagnosis groups, e.g., for the "previously infected group" one specimen was falsely identified as an acute/recent infection. This specimen was counted as a false positive for the "acute/recent infection" group. In the "acute/recent infection" group four patients were falsely identified as being previously infected. These specimens were counted as false positives in the previously infected group.

		Acute/Recent Infection		
		+	-	
Biotrin Parvovirus B19 EIAs	+	15	1	16

Combined Biotrin Parvovirus B19 Enzyme Immunoassay's Positive Predictive Value for the Serological Diagnosis of "acute/recent" parvovirus B19 infection = 93.8% (15/16), 95% CI = 69.8 to 99.8.

		Previously Infected		
		+	-	
Biotrin Parvovirus B19 EIAs	+	143	4	147

Combined Biotrin Parvovirus B19 Enzyme Immunoassay's Positive Predictive Value for the Serological Diagnosis of "previously infected" = 97.3% (143/147), 95% CI = 93.2 to 99.2.

		Not Previously Infected		
		+	-	
Biotrin Parvovirus B19 EIAs	-	3	73	76

Combined Biotrin Parvovirus B19 Enzyme Immunoassay's Negative Predictive Value for the Serological Diagnosis of "not previously infected" = 96.1% (73/76), 95% CI = 88.9 to 99.2.

An overall "acute/recent infection" and "previous infected" "Negative Predictive Value" for the Biotrin assays is calculated as 90.1% (73/73+8).

Interpretation of Assay Results

Based on the above information, the following Interpretation of Results table was established:

Biotrin Parvovirus B19 IgM Serology	Biotrin Parvovirus B19 IgG Serology	Interpretation
IgM Negative	IgG Negative	Implies No Past Infection - patient may be susceptible to infection
IgM Negative	IgG Positive	Implies Past Exposure/ Infection – minimal risk of B19V infection
IgM Equivocal	IgG Positive or Negative	May be indicative of a Current or Recent Infection – resample patient within 1 to 2 weeks and retest.
IgM Positive	IgG Positive	Implies Current or Recent Infection – fetus may be at risk
IgM Positive	IgG Negative or Equivocal	May be indicative of a Current Infection – resample patient within 1 to 2 weeks and retest

If anti-B19V IgG is not detected, then a new specimen should be drawn and reanalyzed for anti-B19V IgM and anti-B19V IgG.

IX. Conclusions

The information and data presented in the non-clinical and clinical studies demonstrate that the Biotrin Parvovirus B19 IgG Enzyme Immunoassay is safe and effective, if used according to the furnished assay procedure and interpretation of assay results, for the indications for use as claimed. The clinical study demonstrated that the most effective use of the Biotrin Parvovirus B19 IgG Enzyme Immunoassay would be when it was used in conjunction with the Biotrin Parvovirus B19 IgM Enzyme Immunoassay.

X. Panel Recommendation

On May 21, 1999, the Microbiology Devices Advisory Panel recommended approval with conditions. The approval conditions were:

- Modification of indication for use statement to incorporate an additional patient population.

- Modification of the labeling's Interpretation of Results section.

- Modification of the labeling's assay Performance Characteristics section to incorporate the assays' performance to "serological diagnosis."

XI. CDRH Action

CDRH agreed with the panel's recommendation. The sponsor modified the labeling to address the panel's concerns. CDRH issued an approval order for the applicant's PMA on

The applicant's manufacturing and control facilities were inspected and the facilities were found to be in compliance with the Good Manufacturing Practice Regulations (GMPs) October 2, 1998.

XII. Approval Specifications

Directions for Use: See labeling.

Conditions of Approval: CDRH approval of this PMA is subject to full compliance with the conditions described in the approval order.

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