P970055

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. General Information

Device Generic Name
Enzyme Linked Immunosorbent Assay, Parvovirus B19 IgM

Device Trade Name
Biotrin Parvovirus B19 IgM 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 IgM Enzyme Immunoassay is intended for the qualitative detection of IgM 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 IgG 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 (formally 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).

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.[3] 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.[4] Cryo-electron microscopy analysis of VP2 capsids alone and complexed to the P antigen have further elucidated the mechanism of B19V infectivity.[5] 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.

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.[6, 7, 8] 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.[9] 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.[10, 11] 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.[12, 13] It is thought that severe fetal anemia, where hemoglobin levels fall to less than 2g/dl, is the primary cause of fetal hydrops.[14] Treatment to date has involved blood transfusion immediately after delivery to overcome the severe anemia associated with congenital infection as well as intrauterine transfusions in the case of hydropic fetuses.[15, 16] Both treatments have met with partial success, however it is notable that B19V induced hydrops can resolve spontaneously and that such intrauterine treatment is not always required.

Exposure of healthy seronegative individuals to B19V results in a typical immune response whereby IgM levels rise soon after infection followed by production of anti-viral IgG with concomitant reduction in serum IgM levels.[7] Elevations in IgG antibody titer have been detected in seropositive individuals when re-exposed to B19V.[7] Immunocompromised individuals may not develop this conventional antibody response and so are more likely to develop chronic viremia.[2]

In the normal host the most widely recognized manifestation of B19V infection is the mild rash illness erythema infectiosum, also called fifth disease. This is typically the fifth rash disease of childhood and is also seen in adults. Erythema infectiosum is usually a mild illness characterized by an intensive erythematous maculopapular facial rash, which gives rise to the use of the term 'slapped cheek disease'. Onset of the rash occurs coincident with production

of B19-specific antibodies suggesting that it is immune mediated.

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 anti-human IgM.

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

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

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

Enzyme Conjugate Concentrate - streptavidin horseradish peroxidase conjugate (10x) in a stabilizing buffer with thimerosal (0.01%).

Enzyme Conjugate Diluent - dilution buffer containing stabilizers and thimerosal (0.01%).

Biotin VP2 Concentrate – concentrated biotinylated recombinant B19V VP2 solution in a buffer containing stabilizers and sodium azide (0.01%).

Biotin VP2 Diluent – diluting buffer containing stabilizers and thimerosal (<0.01%) and sodium azide (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 IgM Enzyme Immunoassay is a mu-capture sandwich enzyme immunoassay for the detection of IgM class antibodies to B19V in human serum and plasma. The IgM in serum or plasma will bind to the rabbit anti-human IgM coated on the wells. Following a wash step, biotinylated B19V recombinant VP2 protein is added that binds to human specific anti-B19V IgM if present. After another wash step, streptavidin

horseradish peroxidase is added which binds to the biotinylated VP2 present. The whole complex is then detected by addition of tetramethylbenzidine substrate (TMB) which turns blue in the presence of peroxidase. A stable yellow end product is achieved by the addition of a stopping reagent.

The recombinant baculovirus-expressed VP2 antigen used in the Biotrin Parvovirus B19 IgM 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.

IV. Contraindications, Warnings and Precautions

There are no known contraindications for the Biotrin Parvovirus B19 IgM 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 IgM include immunofluorescence and Western blot analysis of patient sera.

There are no FDA approved methods for the detection of anti-B19V IgM 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

False positivity

The detection of anti-B19V IgM is indicative of a recent infection with B19V. Any sample which incorrectly tests positive for anti-B19V IgM due to cross-reactivity with the VP2 antigen is termed a false positive. The apparent detection of B19V IgM in these samples can lead to the incorrect diagnosis that recent B19V infection has occurred. If this would occur during pregnancy, this could lead to the initiation of therapy such as passive immunization with serum containing B19V IgG in order to prevent further viral replication. It is

conceivable, therefore, that misdiagnosis may lead to the patient having to undergo unnecessary treatment.

It has been observed that the cause of false positivity in the Biotrin Parvovirus B19 IgM Enzyme Immunoassay may be due to cross-reactivity between the B19V VP2 antigen used in the test and anti-Epstein-Barr Virus IgM. Since the presentation of these two infections vary, it is likely that the clinician will require a full spectrum of laboratory tests so any evidence of a genuine co-infection or assay false positivity will be evident at this stage.

False negativity

False negativity in the Biotrin Parvovirus B19 IgM Enzyme Immunoassay would mean that a recent infection may go undetected. Such an occurrence is unlikely to occur in normal healthy individuals unless the sample for IgM immunodetection is taken at a time when anti-B19V IgM levels are too low to be detected. If clinical evidence of B19V infection is available, any sample giving an unexpectedly negative result for anti-B19V IgM seropositivity should be retested at a later date (2-3 weeks) to recheck the anti-B19V IgM status of the individual. Follow-up of anti-B19V IgG status would also be advisable in such cases to check for any evidence of IgG seroconversion.

False negativity may also occur if the patient is immunocompromised and general immunoglobulin production is suppressed. Any serological result obtained from these individuals must be carefully interpreted.

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 IgM 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 IgM 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 6 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 IgM Enzyme Immunoassay

with and without IgG and IgM absorbents, respectively.

Ten B19V IgM positive sera were tested:

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

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

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

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

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

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

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

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

Assay Cutoff Determination:

The presence or absence of anti-B19V IgM is determined in relation to a calculated Cut Off Value (COV).

To establish the Biotrin Parvovirus B19 IgM Enzyme Immunoassay cut-off Receiver Operating Characteristic (ROC) analysis[17] was performed using a panel of 112 specificity specimens and 110 sensitivity specimens to assess the assay sensitivity and specificity. The majority of the 110 specimens used to establish assay sensitivity were confirmed as anti-B19V IgM positive using an alternative testing methodology as recommended[17] and were obtained from patients known to have been exposed to B19V.

Figure 1 shows the graphical ROC analysis and Table 1 shows the effect of various assay cutoff values on relative sensitivity and specificity.

Figure 1: ROC Analysis of the Biotrin Parvovirus B19 IgM Enzyme Immunoassay.

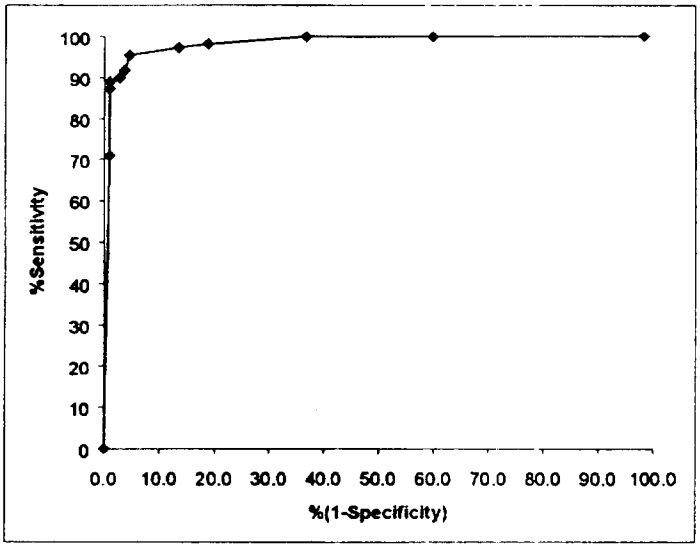

Table 1: Effect of immunoassay cut-off on the relative sensitivity and specificity of the Biotrin Parvovirus B19 IgM Enzyme Immunoassay detection.

Cut Off Index	% Specificity	% Sensitivity
2.0	99.1	70.1
1.1	99.1	87.3
1.0	***99.1***	***89.1***
0.9	97.3	90.0
0.8	96.4	91.8
0.7	96.4	91.8
0.6	95.5	95.5
0.5	86.6	97.3
0.4	81.3	98.2
0.3	63.4	100
0.2	40.0	100
0.1	0.001	100

The current Biotrin Parvovirus B19 IgM Enzyme Immunoassay cut-off is set at an index value of 1.0 which should give 99.1% relative specificity and 89.1% relative sensitivity.

Intra-assay Reproducibility:

A series of specimens, ranging in B19V IgM 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. Table 2 shows the mean OD value, standard deviation, and percentage coefficient of variation.

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Table 2: Intra-assay reproducibility.

Test Specimen	Mean OD	SD	%CV	n
SR-A•	1.460	0.074	5.1	22
SR-B***	1.000	0.020	2.0	22
SR-C*	0.899	0.035	3.9	22
SR-D***	0.896	0.038	4.2	22
MR-E**	0.723	0.030	4.2	22
MR-F•	0.590	0.020	3.4	22
MR-G*	0.529	0.016	3.0	22
WR-H*	0.290	0.010	3.5	22
WR-I•	0.290	0.010	3.5	22
WR-J**	0.280	0.010	3.6	22
UR-K•	0.030	0.002	6.7	22
UR-L•	0.020	0.002	10.0	22

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

The above data in terms of assay index value are given in Table 3.

Table 3: Intra-assay reproducibility expressed in terms of Index values.

Test Specimen	Mean Index	SD	%CV	n
SR-A•	7.710	0.074	1.0	22
SR-B***	6.410	0.070	1.1	22
SR-C*	4.610	0.180	3.9	22
SR-D***	4.600	0.020	0.4	22
MR-E**	2.840	0.120	4.2	22
MR-F•	2.320	0.100	4.3	22
MR-G*	2.080	0.060	2.9	22
WR-H*	1.540	0.050	3.3	22
WR-I•	1.390	0.070	5.0	22
WR-J**	1.490	0.070	4.7	22
UR-K•	0.148	0.006	4.1	22
UR-L•	0.120	0.012	10.0	22

SR: strong reactive, MR: medium reactive, WR: weak reactive, UR: unreactive, • Serum, * EDTA plasma, **Heparinized 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 IgM 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 4). 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 therefore assayed 81 times, with the exception of one strongly reactive specimen that was assayed 79 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 ($y=1.0501$ $x=0.0199$ $r^2=0.99$; $y=0.9691$ $x=-0.112$ $r^2=0.99$; $y=1.0107x-0.1644$ $r^2=0.99$; for site 1 versus 2, site 2 versus 3 and 1 versus 3, respectively).

Table 4: Overall detection rate for the Biotrin Parvovirus B19 IgM Enzyme Immunoassay.

No. of Specimens	Specimen Type	**Detection rate** (Expected result/Total number of times assayed)
5	Strongly reactive	100% (403/403)
7	Weakly reactive	95.5% (542/567)
4	Unreactive	100% (324/324)

When these data are analysed in terms of interassay reproducibility, the Biotrin Parvovirus B19 IgM Enzyme Immunoassay demonstrates good correlation in test results between different laboratories and different master lots. Reproducibility data for eight test specimens is given in Tables 5 and 6.

Table 5: Overall interassay reproducibility. Data (OD) accumulated from 3 test sites and 3 master lots of Biotrin Parvovirus B19 IgM Enzyme Immunoassay.

Specimen	Mean OD	SD	%CV	n
PC	1.862	0.064	3.4	9
LPC	0.411	0.023	5.6	9
NC	0.026	0.004	15.4	9
SR1**	1.201	0.233	19.4	81
SR2•	1.103	0.199	18.0	81
SR3*	1.204	0.229	19.0	79
SR4***	1.539	0.028	1.8	9
WR1•	0.462	0.113	24.5	81
WR2**	0.303	0.090	29.7	81
WR3*	0.407	0.108	26.5	81
WR4***	0.335	0.023	6.9	9

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

Table 6: Overall interassay reproducibility. Data (Index Values) accumulated from 3 test sites/3 master lots of Biotrin Parvovirus B19 IgM Enzyme Immunoassay.

Specimen	Mean OD	SD	%CV	n
NC	0.096	0.013	13.5	9
LPC	1.519	0.082	5.4	9
SR1**	5.493	0.832	15.1	81
SR2•	5.044	0.670	13.3	81
SR3*	5.550	0.653	11.8	79
SR4***	5.666	0.196	3.5	9
WR1•	2.088	0.350	16.8	81
WR2**	1.356	0.234	17.3	81
WR3*	1.834	0.305	16.6	81
WR4***	1.238	0.072	5.8	9

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

Centers for Disease Control and Prevention B19V Serology Panel

Testing of the Centers 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 B19V 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 55% positive and 45% negative anti-B19V IgM samples. The Biotrin Parvovirus B19 IgM Enzyme Immunoassay demonstrated 93.4% 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 86.4% agreement with the positive specimens and 100% agreement with the negative specimens.

Cross-Reactivity

The specificity of the Biotrin Parvovirus B19 IgM Enzyme Immunoassay was assessed by testing specimens from patients with viral infections or disease states which may cause clinical symptoms similar to B19V (Table 7).

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Table 7: Biotrin Parvovirus B19 IgM Enzyme Immunoassay specificity results.

Specimens tested	Number of positives
Cytomegalovirus (CMV)	0/21
Epstein-Barr Virus (EBV)	1/25▲
Rubella virus	0/20
Rubeola virus	0/5
Mumps virus	0/5
Varicella Zoster virus (VZV)	0/5
Human Herpes virus -1	0/5
Human Herpes virus - 2	0/5
Toxoplasma gondii	0/14
Lyme disease	0/5
Thyroiditis	0/5
Rheumatoid Arthritis (RA)	0/5
Lupus erythematosus	0/5
Anti-Nuclear Antibodies (ANA)	2/8▲
Rheumatoid Factor (RF)	0/5
Mycoplasma	0/5
Parainfluenza type 3	0/5
Influenza B	0/4

▲EBV IgM and ANA specimens which were reactive in the Biotrin Parvovirus B19 IgM Enzyme Immunoassay were also tested by B19V immunoblot and immunofluorescent assays and were found to be reactive in both formats. The likelihood of genuine anti-B19V IgM reactivity cannot be excluded.

Clinical Studies

Seroprevalence

A total of 399 samples from two separate US populations (Age range: 17-75) were tested using the Biotrin Parvovirus B19 IgM Enzyme Immunoassay to evaluate the seroprevalence of IgM antibodies to B19V. The data from this seroprevalence study demonstrate that the total rate of anti-B19V IgM positivity is 0.5% (1/200) and 1.5% (3/199). The anti-B19V IgM positivity rate observed is 1% when both populations are combined (n=399). Notably all of the positive samples detected were either in or slightly above the equivocal range of the Biotrin IgM Parvovirus B19 Enzyme Immunoassay. Of the IgM positive samples, one was from a male and 3 were from female donors with an age range of 25 to 45 years. No attempt was made to determine whether the positive results were from recently or acutely infected individuals.

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 IgM Enzyme Immunoassay, the specimens were tested for the presence of anti-B19V IgM 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 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.

An individual was classified as "previously infected" if anti-B19V IgG was detected by at least one reference method and no anti-B19V IgM was detected by any reference method.

The serological diagnosis of "not previously infected" was not finding either anti-B19V IgG or IgM by any of the reference methods.

The above method for interpreting serological results for B19V infection has been published.[10]

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.

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, then 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" B19V 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.

XI. Conclusions

The information and data presented in the non-clinical and clinical studies demonstrate that the Biotrin Parvovirus B19 IgM 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 IgM Enzyme Immunoassay would be when it was used in conjunction with the Biotrin Parvovirus B19 IgG 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 **[XXXXXXXXX]**.

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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