MAR 13 1998

INTEGRATED DIAGNOSTICS, INC. K971591

510(K) SUMMARY
SUMMARY OF SAFETY AND EFFECTIVENESS DATA

INDX[R] DIP-S-TICKS[R] Scrub Typhus Test
For the Detection of IgG and IgM Antibodies to *Orientia tsutsugamushi* (scrub typhus)

NAME AND LOCATION OF MANUFACTURER:

Integrated Diagnostics, Inc. (INDX)
1756 Sulphur Spring Road
Baltimore, MD 21227
Phone (410) 737-8500
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NAME OF CONTACT PERSON:

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President
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DATE OF PREPARATION OF SUMMARY:

April 30, 1997

TRADE NAME OF THE DEVICE:

INDX[R] DIP-S-TICKS[R] Scrub Typhus Test For the Detection of IgG and IgM Antibodies to *Orientia tsutsugamushi* (scrub typhus)

COMMON NAME:

DIP-S-TICKS[R] Scrub Typhus Test

CLASSIFICATION NAME:

Rickettsia serological reagents, 21 CFR 866.3500

LEGALLY MARKETED DEVICE (PREDICATE DEVICE) TO WHICH THE MANUFACTURER IS CLAIMING SUBSTANTIAL EQUIVALENCE:

INDX Indirect Immunofluorescence (IFA) Slide Test for the Detection of Antibodies to Rickettsial Species (*O. tsutsugamushi*). In this notification, comparisons were also made to the Indirect Immunoperoxidase (IIP) method, which is identical to the IFA test, except for the use of a fluorescence rather than an enzyme-conjugated substrate on a prepared slide. The IIP method enables the use of a light microscope for antibody detection rather than a fluorescence microscope.

DESCRIPTION OF THE DEVICE:

The INDX[R] DIP-S-TICKS[R] Scrub Typhus Test For the Detection of IgG and IgM Antibodies to *Orientia tsutsugamushi* (scrub typhus) utilizes an enzyme-linked immunoassay (ELISA) dot-blot technique for the detection of IgM as well as total (IgM and IgG) dengue antibodies. The antigen is dispensed as discrete dots onto a solid membrane. After adding specimen to a reaction vessel, an assay strip is inserted, allowing patient antibodies reactive with the test antigen to bind to the strip's solid support membrane. In the second stage, the reaction is enhanced by removal of non-specifically bound materials. During the third stage, alkaline phosphatase-conjugated anti-human IgG/IgM antibodies are allowed to react with bound patient antibodies. Finally, the strip is transferred to enzyme substrate reagent, which reacts with bound alkaline phosphatase to produce an easily seen, distinct spot.

INTENDED USE OF THE DEVICE:

The INDX[R] DIP-S-TICKS[R] Scrub Typhus Test For the Detection of IgG and IgM Antibodies to *Orientia tsutsugamushi* (scrub typhus) is a semi-quantitative enzyme immunoassay for the **detection of total IgG and IgM antibodies to *Orientia tsutsugamushi*,** for the serological confirmation of scrub typhus in samples of serum, plasma or heparinized whole blood. This test is intended to be performed by trained medical technologists only.

SUMMARY OF THE TECHNICAL CHARACTERISTICS OF THE MANUFACTURER'S DEVICE COMPARED TO THE PREDICATE DEVICE:

COMPARISONS OF INDX DIP-S-TICKS AND REFERENCE METHODS

No.	Item Comparison	INDX Device	Reference Device(s)	Comparison
1.	Intended Use	Detection of scrub typhus antibody	Detection of scrub typhus antibody	Substantially equivalent
2.	Agent Measured	*O. tsutsugamushi*	*O. tsutsugamushi*	Substantially equivalent
3.	Disease and phase of disease	Scrub typhus, acute and convalescent phases	Scrub typhus, acute and convalescent phases	Substantially equivalent
4.	Specificity	IgG and IgM Antibody to Agent	IgG and IgM Antibody to Agent	Substantially equivalent
5.	Format	EIA dot-blot	Indirect Immunofluorescence (IFA) or Immunoperoxidase (IIP)	Substantially equivalent
6.	Endpoint detection method	Enzyme-substrate and conjugate in a solid phase	Enzyme-substrate or fluorescent substrate on a prepared slide	Substantially Equivalent
7.	Use of results	Semi-quantitative	Semi-quantitative	Substantially equivalent
8.	Sample prep. methods	heparinized serum plasma or whole blood	serum	Substantially equivalent
9.	Positive and Negative Controls	Required and Included	Required and Included	Substantially equivalent
10.	Summary of Comparisons	Average Sensitivity for Comparisons of 91.4% Average Specificity for Comparisons of 89.1% Average Agreement for Comparisons of 89.5%		Substantially equivalent

NON-CLINICAL TESTS SUPPORTING A DETERMINATION OF SUBSTANTIAL EQUIVALENCE:

Expected Values

The number of antibody positive subjects in a population depends on two factors: disease prevalence and clinical criteria used to select the tested population. Because very few positives should be seen in a randomly screened population in a non-endemic area, most serology tests are not specific enough to screen non-endemic populations. Even in an endemic region, serology screening often yields many false positives if used to randomly screen patients. Serology tests are useful to test patients in an endemic region with signs and symptoms consistent with the disease.

Antibody levels are generally low or absent during very early infection. Symptomatic patients may have no antibody during the first 1-2 weeks after exposure and the antibody titer will rise with time.

Normal Population

Sera obtained from a total of ten (10) asymptomatic normal donors were evaluated with the DIP-S-TICKS method in this study. All sera had a negative IFA result for scrub typhus and were subsequently evaluated by the dot-blot method. All of 10 sera were negative or non-reactive to the dot-blot method.

Negative Patient Control Sera: (Presumptive Negatives)

The following table summarizes the results of the study, and indicates the types of non-rickettsial diseases, number of sera evaluated for each disease, and results of the DIP-S-TICKS dot-blot test for scrub typhus. In this study, the DIP-S-TICKS test showed a negative result in 49 of 51 sera that were confirmed not to have scrub typhus, and was positive in 2 of the 51 sera. Only one of the positive samples (malaria) is a tropical disease that might be encountered in the same geographic environment as scrub typhus.

DISEASE	NUMBER OF SERA TESTED	DIP-S-TICKS NEGATIVE	DIP-S-TICKS POSITIVE
Rheumatoid Factor	10	9	1
Antinuclear Antibody	11	11	0
Malaria	6	5	1
Bartonellosis	6	6	0
Leptospirosis	6	6	0
Typhoid	3	3	0
Cholera	9	9	0
TOTAL	51	49	2

Precision Study:

The Kato/Gilliam antigen is included in the DIP-S-TICKS test strip at a screening dilution and is scored as either positive or negative. In precision studies, reactions were graded as 0 dot (negative), 0.5 dots (equivocal) and 1 dot (positive). Replicate tests conducted within the same day using standard non-immune sera consistently resulted in 0 dot (negative) reaction. The following data are representative of studies of replicate test strips conducted within the same day with the indicated Kato/Gilliam positive human immune sera. Sera listed more than once represent the evaluation of strips on separate days.

Sera No.	Mean Response (No. of dots)	S.D.	Range	n
S0023	0.6	±0.2	0.5-1.0	11
S0023	0.6	±0.2	0.5-1.0	11
S0024	0.8	±0.2	0.5-1.0	11
S0024	1.0	±0.0	1.0-1.0	9
S0025	1.0	±0.0	1.0-1.0	15
HAS	1.0	±0.0	1.0-1.0	15

The Karp antigen is included in the DIP-S-TICKS test strip at 3 dilutions in the range of 1:400 to 1:6400 or greater. This range of Karp antigen is intended to permit an assessment of the relative *O. tsutsugamushi* antibody strength to which the Karp antigen reacts. The antibody strength is indicated by the number of positive Karp antigen dots observed. In precision studies, replicate tests conducted within the same day using standard non-immune sera consistently resulted in 0 dot (negative) reaction. The following data are representative of studies of replicate test strips conducted within the same day with the indicated Karp positive human immune sera. Sera listed more than once represent the evaluation of strips on separate days.

Sera No.	Mean Response (No. of dots)	S.D.	Range	n
S0023	2.5	±0.0	2.5-2.5	11
S0023	2.6	±0.2	2.5-3.0	11
S0023	3.0	±0.0	3.0-3.0	9
S0024	2.5	±0.0	2.5-2.5	9
S0024	2.3	±0.2	2.0-2.5	11
HAS	2.5	±0.1	2.0-2.5	15

CLINICAL TESTS SUPPORTING A DETERMINATION OF SUBSTANTIAL EQUIVALENCE:

Comparison Studies

Study No. 1 Comparison of Methods On 91 Febrile Sera from NorthCentral Malaysia

A group of 91 presumptive positive samples were tested. All samples were obtained from a U.S. medical reference laboratory for rickettsial diseases. The samples were acquired retrospectively from 56 clinical cases of febrile patients in North Central peninsular Malaysia.

The 91 presumptive positive samples were analyzed for the presence of scrub typhus antibodies by the DIP-S-TICKS Dot-Blot and indirect immunofluorescence (IFA) methods. Both methods detect the presence of IgM and IgG antibodies.

Performance Characteristics for 91 febrile samples:

SENSITIVITY = 90.4%
SPECIFICITY = 66.7%
AGREEMENT = 80.2%

Results of Semi-Quantitative Comparisons for 91 febrile samples:

The semi-quantitative relationship between the number of positive Karp strain *O. tsutsugamushi* DIP-S-TICKS dots and the inverse of geometric means of IFA titers was determined for the group of 91 febrile sera. For the IFA method, the IgG and IgM scrub typhus titers are reported separately. The DIP-S-TICKS method detected total (IgG and IgM) scrub typhus antibodies. These data are shown in the following table. As the table indicates, the inverse of geometric mean titers for IgM and for IgG consistently increased as the number of positive dots increased. However, the range of IFA IgG titers is much larger than the range of IFA IgM titers and better discrimination between IgG titers is possible when comparing to the corresponding number of DIP-S-TICKS dots. The differences shown were statistically significant between 0, 1 and 2 or 3 dots for IgG. The differences shown were statistically significant between 0 and 3 dots for IgM.

Geometric means of inverse indirect immunofluorescence (IFA) titers for each level of DIP-S-TICKS response using the Karp strain of O. tsutsugamushi antigen in tests of 91 clinical sera

No. of Positive dots on the DIP-S-TICKS	Inverse of Geometric Mean IFA Titer	
	IgG	IgM
0	6.1 †	2.3 †
1	26.5 †	3.5 †‡
2	183.8 ‡	4.1 †‡
3	98.0 ‡	9.7 ‡

Means in a column not followed by the same symbol were significantly different ($P<0.05$) in Duncan's multiple range test. Analysis of variance of IgG means: $F = 22.5$, degrees of freedom (df) = 3/86, $P < 0.001$. Analysis of variance of IgM means: $F = 0.17$, df = 3/86, $P = 0.18$. Inverse titers were transformed to logs and analysis of variance (ANOVA) followed by Duncan's test performed to test whether the titers corresponding to 1, 2 or 3 positive dots were significantly different.

These data demonstrated the semi-quantitative relationship between the number of DIP-S-TICKS dots observed and the inverse geometric mean IFA titers for the detection of IgG and IgM scrub typhus antibodies.

Study No. 2: Comparison of Methods On Sera From 60 Febrile Patients from Northern Thailand

This study was based on the comparison of the DIP-S-TICKS dot-blot and immunoperoxidase (IIP) methods for the detection of IgG and IgM antibodies to *O. tsutsugamushi*. Samples of 60 sera from febrile patients were obtained prospectively from the Chiangrai Hospital in Thailand. Previous studies at this institution with the IIP method indicated that IgG antibody titers of 1:1600 or greater, or IgM titers of 1:1400 or greater in a single serum specimen were indicative of active scrub typhus.

Performance Characteristics of the DIP-S-TICKS test for 60 febrile samples:

SENSITIVITY = 100.0%
SPECIFICITY = 95.5%
AGREEMENT = 96.7%

Study No. 3: Comparison of Methods On Sera From 83 Febrile Patients from North-East Thailand

This study was based on the comparison of the DIP-S-TICKS dot-blot and immunoperoxidase (IIP) methods for the detection of IgG and IgM antibodies to *O. tsutsugamushi*. Sera samples from 83 febrile patients were obtained were obtained at the Mahara Hospital in Nakhon Ratchasima province of North-East Thailand.

This prospective study was conducted between November, 1995 and January, 1996. Patients were admitted to the hospital based on symptoms including fever of unknown origin. Blood was drawn from each patient on the first symptomatic day (day 0). Convalescent sera were also obtained during a followup two weeks from day 0 (day 14). Patients were evaluated on a daily basis. Day 0 and convalescent sera from each donor were stored at -70°C when drawn, and were thawed immediately prior to simultaneous testing by the DIP-S-TICKS and IIP methods.

Performance Characteristics of the DIP-S-TICKS test for 83 febrile samples:

SENSITIVITY = 86.7%
SPECIFICITY = 94.3%
AGREEMENT = 91.6%

Study No. 4: Comparison of Methods On 28 Paired Acute and Convalescent Sera from NorthCentral Malaysia

Twenty eight (28) pairs of acute and convalescent sera were obtained and evaluated as an extension of the study described in *Study No. 1*, of febrile patients in NorthCentral Malaysia. These samples from febrile patients were used to compare the DIP-S-TICKS and indirect immunofluorescence (IFA) methods. The acute sample was obtained as soon as possible after the appearance of fever, and the convalescent sample was obtained approximately 2 weeks thereafter. Samples were immediately frozen at -20°C, and acute and convalescent samples were evaluated simultaneously.

The diagnosis of active disease requires a 4-fold rise in antibody titer, when acute and convalescent samples are compared, for a positive DIP-S-TICKS or IFA test. In the IFA test, a 4-fold rise in titer to or greater than 1:64 is indicative of a positive response, to rule out the detection of antibody remaining from a prior scrub typhus infection. An increase in the number of positive dots in the DIP-S-TICKS test from 1-2, 2-3 or >3 dots denotes a 4-fold increase, since the *O. tsutsugamushi* antigen is diluted 4 fold for each antigen dot.

Performance Characteristics of the DIP-S-TICKS test compared to the IFA test for 28 paired sera samples:

SENSITIVITY = 88.5%
SPECIFICITY = 100.0%
AGREEMENT = 89.3%

In summary, four independent studies of the comparison of the DIP-S-TICKS and either the IFA or IIP predicate methods were conducted on a total of 262 sera samples from febrile patients. In these studies, either single samples (3 studies and 234 sera) or paired acute and convalescent samples (1 study and 28 sera) formed the basis for comparison. The overall comparison of methods was as follows:

STUDY	SENSITIVITY	SPECIFICITY	AGREEMENT BETWEEN METHODS	n
No. 1	90.4	66.7	80.2	91
No. 2	100.0	95.5	96.7	60
No. 3	86.7	94.3	91.6	83
No. 4	88.5	100.0	89.3	28
Mean	91.4	89.1	89.5	
± 1 S.D.	5.9	15.2	6.9	

BIBLIOGRAPHY

1. Elisberg, BL and FM Bozeman, The Rickettsiae. in Diagnostic Procedures for Viral, Rickettsial and Chlamydial Infections, 5th Ed. Eds. EH Lennetts & NJ Schmidt, pp 1061-1099, 1979.
2. Centers for Disease Control, 1981. Rickettsial Surveillance Report No. 2. Summary: 1979. U.S. Department of Health and Human Services, Washington, D.C.
3. Fiset, P. "Clinical Laboratory Diagnosis of Rickettsial Disease of Man" in *Handbook of Clinical Laboratory Science,* Vol. 1, Part 2, Hsuing, G.D. and Green, R.H. Eds., CRC Press, West Palm Beach, Florida, p361-366, 1978.
4. Centers for Disease Control/National Institutes of Health Manual Biosafety in Microbiological and Biomedical Laboratories, 1984.
5. Brown G.W., Scrub typhus: pathogenesis and clinical syndrome, In Walker D.H., (ed), Biology of Rickettsial Diseases, Vol. 1, p. 93-100, CRC Press, Inc. Boca Raton, 1988.
6. Strickman D., Serology of scrub typhus: New directions for an old disease, Clin. Immunol. Newsletter 14:(5)62-65, 1994.
7. Strickman D., Tanskul P., Eamsila C. et al, Prevalence of antibodies to rickettsiae in the human population of suburban Bangkok, Am. J. Trop. Med. Hyg. 51:149-153, 1994.
8. Brown G.W., Shirai A., Rogers C. et al, Diagnostic criteria for scrub typhus: Probability values for immunofluorescent antibody and *Proteus* OXK agglutinin titers, Am. J. Trop. Med. Hyg. 32(5):1101-1107, 1983.
9. Weddle J.R., Chan T.C., Thompson K. et al, Effectiveness of a dot-blot immunoassay of anti-*Rickettsia tsutsugamushi* antibodies for serological analysis of scrub typhus, Am. J. Trop. Med. Hyg. 53(1):43-46, 1995.
10. Chouriyagune C.,Watt G., Strickman D., Jinasen R., The Weil-Felix test for the diagnosis of scrub typhus in Thailand, Intern. Med. 8:29-32, 1992.
11. Kelly D.J., Serologic diagnosis of rickettsial diseases, Clin. Immunol. Newsletter 14:57-61, 1994.
12. Kelly D.J., Wong P.W., Gan E. et al, Multi-laboratory evaluation of a scrub typhus diagnostic kit, Am. J. Trop. Med. Hyg. 43:301-307, 1990.
13. McDade J.E., Fishbein D.B., Rickettsiaceae: the rickettsiae, In E.H. Lennette, P. Halonen, F.A. Murphy (Eds.), Laboratory diagnosis of infectious diseases, Principles and practice, Vol II, p. 864-890, New York, Springer-Verlag, 1988.
14. Wisseman C.L., Scrub typhus, In Strickland, G.T. (ed.) Hunter's Tropical Medicine (6th Edition), p. 221-223, Philadelphia, W.B. Saunders, 1991.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

MAR 13 1998

Integrated Diagnostics, Inc.
c/o David C. Bishop, Ph.D.
Consultant to INDX
605 Dilworth Road
Downingtown, PA 19335

Re: K971591
Trade Name: INDX Dip-S-Ticks Scrub Typhus Test
Regulatory Class: I
Product Code: LSQ
Dated: December 22, 1997
Received: December 24, 1997

Dear Dr. Bishop:

We have reviewed your Section 510(k) notification of intent to market the device referenced above and we have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (Premarket Approval), it may be subject to such additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 895. A substantially equivalent determination assumes compliance with the Current Good Manufacturing Practice requirements, as set forth in the Quality System Regulation (QS) for Medical Devices: General regulation (21 CFR Part 820) and that, through periodic QS inspections, the Food and Drug Administration (FDA) will verify such assumptions. Failure to comply with the GMP regulation may result in regulatory action. In addition, FDA may publish further announcements concerning your device in the Federal Register. Please note: this response to your premarket notification submission does not affect any obligation you might have under sections 531 through 542 of the Act for devices under the Electronic Product Radiation Control provisions, or other Federal laws or regulations.

Under the Clinical Laboratory Improvement Amendments of 1988 (CLIA-88), this device may require a CLIA complexity categorization. To determine if it does, you should contact the Centers for Disease Control and Prevention (CDC) at (770)488-7655.

This letter will allow you to begin marketing your device as described in your 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801 and additionally 809.10 for in vitro diagnostic devices), please contact the Office of Compliance at (301) 594-4588. Additionally, for questions on the promotion and advertising of your device, please contact the Office of Compliance at (301) 594-4639. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR 807.97). Other general information on your responsibilities under the Act may be obtained from the Division of Small Manufacturers Assistance at its toll free number (800) 638-2041 or at (301) 443-6597 or at its internet address "http://www.fda.gov/cdrh/dsmamain.html"

Sincerely yours,

Steven Gutman

Steven I. Gutman, M.D., M.B.A.
Director
Division of Clinical Laboratory Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosure

Page____of____

510(k) Number (if known): K971591

Device Name: INDX Dip-S-Ticks Scrub Typhus Test

Indications For Use:

INDICATIONS FOR USE:

The INDX® Dip-S-Ticks® scrub typhus test is an enzyme immunoassay for use as an aid in the diagnosis of scrub typhus, and detects total IgG and IgM antibodies to *Orientia tsutsugamushi*. The Dip-S-Ticks test is qualitative when used to test a single specimen; when using paired specimens to detect sero-conversion the test may be semi-quantitative. The test is intended for use in serum as well as heparinized plasma, whole blood and finger-stick capillary blood and is intended to be performed by trained medical personnel only.

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

(Division Sign-Off)
Division of Clinical Laboratory Devices
510(k) Number K971591

Prescription Use____ OR Over-The-Counter Use____
(Per 21 CFR 801.109)

(Optional Format 1-2-96)