

FEB 23 2000

I. 510(k) Summary

510(k) number: K994356

This summary of 510(k) safety and effectiveness information is being submitted in accordance with the requirements of SMDA 1990 and 21 CFR §807.92.

A. Submitter's information

Name: DiagnoCure Inc.
Address: 2050 René-Lévesque Ouest, 6th floor
Sainte-Foy, Québec
Canada, G1V 2K8
Telephone: 418-527-6100
Fax Number: 418-527-0240
Contact person: Pierre Pelletier
Date prepared: February 7, 2000

B. Device information

Name of device: ImmunoCyt
Trade name: ImmunoCyt™
Common Name: Immunocytofluorescence assay
Classification Name: Immunohistochemistry kit

C. Predicate devices

ImmunoCyt is substantially equivalent to these currently marketed devices:

#1 Predicate Device: Bard BTA stat Test
Manufacturer: Bainbridge Sciences Inc.,
Subsidiary of C.R. Bard Inc.
Redmond, Washington
510(k) Number: K964151

#2 Predicate Device: Auratek FDP
Manufacturer: Organon Teknika, B.V.
Applicant: Perimmune Inc.
1330 Piccard Dr.
Rockville, MD 20850
510(k) Number: K970353

Note: Auratek FDP is marketed in the US under the name Accu-Dx

D. Device description

ImmunoCyt is an *in vitro* diagnostic device that contains a solution of three monoclonal antibodies. Two antibodies are reactive to epitopes selectively detected on a mucin found in bladder cancer cells, and one antibody reacts with a bladder cancer-associated glycosylated form of the carcinoembryonic antigen. The antibodies are coupled with fluorescent markers. This solution is used to detect tumor cells exfoliated in the urine of bladder cancer patients.

ImmunoCyt also contains a sample fixative and a blocking solution, as well as positive and negative control cells. The purpose of the blocking solution is to minimize non-specific binding of the antibodies. The purpose of the sample fixative is to optimize the quality of the cells isolated from urine by stabilizing the pH and decreasing crystals, mucus and other potential sources of artifacts in staining. Positive and negative control cells are to be used with each test sample preparation as qualitative indicators of the adequacy of the technique, reagents and instruments.

E. Intended use and indications

ImmunoCyt is a qualitative direct immunocytofluorescence assay intended for use in conjunction with cytology to increase the overall sensitivity for the detection of tumor cells exfoliated in the urine of patients previously diagnosed with bladder cancer. ImmunoCyt is indicated for use as an aid in the management of bladder cancer in conjunction with urinary cytology and cystoscopy.

F. Technological characteristics

ImmunoCyt, the *in vitro* diagnostic device presented in this 510(k) submission is substantially equivalent to two currently marketed devices: the AuraTek FDP and the BARD BTA *stat* Test. All three devices are indicated to measure the presence of bladder-associated markers in the urine of patients already diagnosed with bladder cancer, and are based upon the use of antibodies. However, the analytes detected in each system are different. All three devices are indicated for use in conjunction with cystoscopy.

Substantial equivalence comparison table

Intended use	ImmunoCyt is a qualitative direct immunocytofluorescence assay intended for use in conjunction with cytology to increase the overall sensitivity for the detection of tumor cells exfoliated in the urine of patients previously diagnosed with bladder cancer.	The Bard BTA stat test is an <i>in vitro</i> immunoassay intended for the qualitative detection of bladder tumor associated antigen in urine of persons diagnosed with bladder cancer.	AuraTek FPD is a rapid one-step gold dye particle lateral flow immunoassay indicated for the <i>in vitro</i> qualitative measurement of fibrinogen and fibrin/fibrinogen degradation products (FDP) in human urine.
Indication	Indicated for use as an aid in the management of bladder cancer in conjunction with urinary cytology and cystoscopy.	Indicated for use as an aid in the management of bladder cancer patients, in conjunction with cystoscopy.	To be used with standard cystoscopic examination to aid in the management of patients with a history of bladder cancer.
Format	Immunocytofluorescence assay	Immunoassay	Immunoassay
Reagents	Antibody-based	Antibody-based	Antibody-based
Sample Matrix	Urine	Urine	Urine
Analyte	Cell-associated antigens M344, LDQ10, 19A211	A human complement factor H-related protein	Fibrinogen and Fibrin/fibrinogen degradation products
Sensitivity	94%	66%	67%
Specificity	50%	80%	70%

The three tests are intended to detect the presence of bladder tumors through urine sample analysis, but they each measure a different substance. All three analytes are all related to the presence of bladder tumors.

G. Summary of studies

Clinical performance

Samples were collected from 14 hospital centers in Canada and were mixed with an equivalent volume of ethanol and stored refrigerated until processing at DiagnoCure's laboratories in Sainte-Foy (Québec), Canada. The clinical sensitivity of ImmunoCyt was established using urine samples from a panel of 87 patients with bladder tumor recurrences confirmed by histology. The clinical specificity of ImmunoCyt was established using urine samples from a panel of 154 patients with negative cystoscopy while being followed for bladder tumor recurrence. Specificity was also tested on urine samples from a panel of 170 normal individuals (without genitourinary symptoms) and on urine samples from a panel of 100 patients with various genitourinary disorders other than bladder cancer, as established by cystoscopy.

Sensitivity Results by Stage and Grade (percentage)

Grade	N	P	L _L	L _U	P	L _L	L _U	P	L _L	L _U
1	21	38.1	19.0	61.3	95.2	74.1	99.8	95.2	74.1	99.8
2	45	48.9	33.9	64.0	93.3	80.7	98.3	97.8	86.8	99.9
3	21	66.7	43.1	84.5	95.2	74.1	99.8	100	86.7	100
Stage										
Ta	52	46.2	32.5	60.4	96.2	85.7	99.3	96.2	85.7	99.3
T1	23	43.5	23.9	65.1	95.7	76.0	99.8	100	87.8	100
T2*	7	85.7	42.0	99.2	85.7	42.0	99.2	100	65.2	100
Tis	5	80.0	29.9	98.9	80.0	29.9	98.9	100	54.9	100
Total	87	50.6	39.7	61.4	94.3	86.5	97.9	97.7	91.2	99.6

Key to tables 1, and 2:

N: Number; P: Proportion; L_L: Lower bound of 95% confidence interval; L_U: Upper bound of 95% confidence interval

Specificity Results by Condition (percentage)

Condition	N	P	L _L	L _U	P	L _L	L _U	P	L _L	L _U
Normal asymptomatic	170	100	98.3	100	77.1	69.9	83.0	77.1	69.9	83.0
GU disorders										
Prostate cancer	15	100	81.9	100	46.7	22.3	72.6	46.7	22.3	72.6
Inflammation	24	100	88.3	100	62.5	40.8	80.5	62.5	40.8	80.5
BPH	25	100	88.7	100	32.0	15.7	53.6	32.0	15.7	53.6
Hematuria	13	100	79.4	100	46.2	20.4	73.9	46.2	20.4	73.9
Lithiasis	8	100	68.8	100	37.5	10.2	74.1	37.5	10.2	74.1
GU conditions*	15	100	81.9	100	46.7	22.3	72.6	46.7	22.3	72.6
Total	100	100	97.0	100	46.0	36.1	56.2	46.0	36.1	56.2
Monitored for bladder cancer with no evidence of disease	154	94.8	89.7	97.6	50.0	41.9	58.1	49.4	41.3	57.5

*: Various genitourinary disorders including: vesical atony, urinary incontinence, functional urinary dysfunction, irritative bladder, hydronephrose, urethrocele, prostatism, urethral diverticula, cystocele, urinary retention, and hematuria.

Comparison of ImmunoCyt and Cystoscopy in Detection of Recurrent Bladder Cancers

Positive	82	77	159
Negative	5	77	82
Total	87	154	241

Monitoring sensitivity: 94.3% (86.5-97.9%, 95% confidence interval)
 Monitoring specificity: 50.0% (41.9-58.1%, 95% confidence interval)

2. Reproducibility

Within-reader variability was determined using three readers from three different laboratories, each performing triplicate and blinded reading of one panel of three patient slides and one panel of three mock samples slides, one slide for each level of positivity in both panels. Between-reader variability was determined using nine readers from three different laboratories, each reader performing single and blinded reading of a panel of nine mock samples slides, three slides for each level of positivity. Between-laboratory variability was determined using three readers from three different laboratories, each reader performing single and blinded reading of a panel of twelve patient slides, four slides for each level of positivity.

Descriptive statistics

Reader	Sample	Level	0	1	2	3	4	5	6	7	8	9	10	11	12
Within Reader	Mock Samples	-	0	4	0.44	1.33	0	0	0.00	0.00					
		+	0	16	5.11	5.51	0	3	1.33	1.12					
		++	7	31	21.67	10.01	1	17	9.11	6.17					
Between Reader	Mock Samples	-	0	9	0.41	1.74	0	2	0.19	0.56					
		+	0	18	5.44	6.62	0	9	1.67	2.27					
		++	7	81	35.26	22.74	3	65	14.70	12.22					
Within Reader	Patient Slides	-	0	1	0.33	0.50	0	0	0.00	0.00					
		+	1	13	6.00	4.44	1	21	6.11	6.49					
		++	1	5	1.78	1.39	1	193	54.67	61.01					
Between Lab.	Patient Slides	-	0	1	0.17	0.39	0	4	0.67	1.37					
		+	0	5	2.75	1.96	0	4	0.83	1.19					
		++	0	9	2.67	3.73	1	30	12.83	9.86					

Concordance rates

Sample	Level	Reader	Agree	Disagree	Agree	Disagree	Agree	Disagree	Agree	Disagree	Agree	Disagree	Agree	Disagree	Agree	Disagree
Mock Samples	-	Within Reader	3/3	3/3	2/3	8/9	89% (51.8%-99.7%)									
		Between Reader	8/9	9/9	6/9	23/27	85% (66.3%-95.8%)									
	+ / ++	Within Reader	6/6	6/6	3/6	15/18	83% (58.6%-96.4%)									
		Between Reader	12/18	18/18	17/18	47/54	87% (75.1%-94.6%)									
Patient Slides	-	Within Reader	3/3	0/3	3/3	6/9	67% (29.9%-92.5%)									
		Between Laboratory	3/4	4/4	0/4	7/12	58% (27.7%-84.8%)									
	+ / ++	Within Reader	6/6	6/6	6/6	18/18	100% (81.5%-100%)									
		Between Laboratory	7/8	8/8	8/8	23/24	96% (78.9%-99.9%)									
Total	- / + / ++	All	48/57	54/57	45/57	147/171	86% (80.8%-91.2%)									

3. Interfering substances

Testing has been conducted to identify cross-reactivity between the ImmunoCyt kit and potential contaminants in urine specimens. The specific objectives were to establish whether the presence of contaminants: 1) induced false positivity on negative samples, and 2) extinguished positivity on positive samples. Proteinaceous contaminants included white blood cells, red blood cells, albumin, and immunoglobulin. All were from human origin. Microbial contaminants included: *Candida albicans*, *Escherichia coli*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*. All microbial contaminants came from ATCC. Each test condition was conducted on three urine samples from different donors or patients, and at two pH levels (5.0 and 8.0).

Interfering Substances

Albumin	10 mg	10 mg
γ -globulin	0.625 mg	0.625 mg
White blood cells	5×10^4 cells	5×10^4 cells
Red blood cells	1×10^6 cells	1×10^6 cells
<i>Candida albicans</i>	1×10^8 cells	1×10^8 cells
<i>Escherichia coli</i>	1×10^8 cells	1×10^8 cells
<i>Staphylococcus aureus</i>	1×10^8 cells	1×10^8 cells
<i>Pseudomonas aeruginosa</i>	1×10^8 cells	1×10^8 cells

The effects of intravesical therapy with BCG or chemotherapy on the specificity of ImmunoCyt have not been established. Test results from samples of patients who have received such should be treated carefully.

H. Conclusions

The safety and effectiveness data demonstrate how the performance of ImmunoCyt compares to the legally marketed devices, Bard BTA *stat* test and AuraTek FDP. Furthermore, the data substantiate the basic performance claim of the product, e.g. to increase the overall sensitivity of urinary cytology for the detection of tumor cells exfoliated in the urine of patients previously diagnosed with bladder cancer.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

FEB 23 2000

DiagnoCure, Inc.
c/o Dr. Bruce F. Mackler
Heller Ehrman White and McAuliffe, LLP
815 Connecticut Avenue, N.W., Suite 200
Washington, D.C. 20006-4004

Re: K994356
Trade Name: ImmunoCyt™
Regulatory Class: II
Product Code: NBK
Dated: December 22, 1999
Received: December 23, 1999

Dear Dr. Mackler:

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 legally marketed predicate 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.

Page 2

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" (21CFR 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 (301) 443-6597 or at its internet address "<http://www.fda.gov/cdrh/dsma/dsmamain.html>".

Sincerely yours,



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

Indications for Use Statement

Applicant: DiagnoCure Inc.

510(k) Number (if known): K994356

Device Name: ImmunoCyt

Indications for use:

ImmunoCyt is a qualitative direct immunocytofluorescence assay intended for use in conjunction with cytology to increase the overall sensitivity for the detection of tumor cells exfoliated in the urine of patients previously diagnosed with bladder cancer. ImmunoCyt is indicated for use as an aid in the management of bladder cancer in conjunction with urinary cytology and cystoscopy.



(Division Sign-Off)
Division of Clinical Laboratory Devices K994356
510(k) Number _____

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

Concurrence of CDRH, Office of Device Evaluation (ODE)

Prescription Use ✓
(Per 21 C.F.R. 801.109)

OR

Over-The-Counter Use _____
(Optional Format 1-2-96)