

K904151

APR 16 1997

510(k) SUMMARY INFORMATION

This 510(k) summary information is being submitted in accordance with the requirements of SMDA 1990 and 21 CFR 807.92. The following information provides sufficient detail to understand the basis for a determination of substantial equivalence.

A. Submitter's Information:

Submitter's Name:	Bard Diagnostic Sciences, Inc.
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Date of Preparation:	September 11, 1996

B. Device Name:

Trade Name:	Bard® BTA <i>stat</i> TM Test
Common / Usual Name:	BTA <i>stat</i> TM Test
Classification Name:	Tumor Associated Antigen Immunological Test System

C. Predicate Device Name:

Trade Name:	Bard® BTA® Test P940018 - Reclassified to Class II
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Bard Diagnostic Sciences, Inc., claims substantial equivalence to the above mentioned test.

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Bard BTA *stat* Test

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D. **Device Description:** The BTA *stat* test for bladder tumor associated antigen is an immunochromatographic assay utilizing monoclonal antibodies to specifically detect the presence of bladder tumor associated antigen in urine. Patient urine is added to the sample well and allowed to react with a colloidal gold-conjugated antibody. If the antigen is present in the sample, an antigen conjugate complex is formed and a line in the patient (P) test zone appears.

E. **Intended Use:**

The BTA *stat* test is an *in vitro* diagnostic immunoassay indicated for the qualitative detection of bladder tumor associated antigen in urine of persons diagnosed with bladder cancer. This test is indicated for use as an aid in the management of bladder cancer patients in conjunction with cystoscopy.

F. **Indications for Use:**

The BTA *stat* test is a qualitative test indicated for use as an aid in the management of bladder cancer patients in conjunction with cystoscopy.

G. **Substantial Equivalence & Technological Characteristics Summary:**

The Bard BTA *stat* Test and the Bard BTA Test are both rapid format qualitative assays. The Bard BTA *stat* test is a lateral flow assay which detects antigen through antigen-specific antibodies. The Bard BTA Test is a test strip assay which detects "bladder tumor associated analytes" through an agglutination interaction with IgG coated latex particles. Both assays are intended for management of bladder cancer patients, but they detect different substances.

EXPECTED RESULTS

CLINICAL SENSITIVITY

BTA stat test sensitivity (Table I) was determined using urine samples from 220 patients with biopsy confirmed bladder tumor recurrence. Samples were collected from 5 different geographic locations throughout the United States and stored frozen until tested. Testing of samples for this study was performed at Bard Diagnostic Sciences, Inc. The average patient age was 68 years, 78% were males, 67% caucasian, 1% African American, 4% Asian, Hispanic or other, and 27% of unknown ethnicity. Results are presented below by stage and by grade of the tumor.

Table I. BTA stat TEST SENSITIVITY BY STAGE AND GRADE*

STAGE	N	SENSITIVITY (%)
Ta	111	51
T1	36	80
≥T2	50	68
Tis	18	61
GRADE	N	SENSITIVITY (%)
1	57	42
2	56	66
3	95	89

*3 patients without stage and 12 without grade determinations.

A subset of the patients studied (181) also had the Bard BTA test performed on the same sample as the BTA stat test. In this study the Bard BTA test had a sensitivity of 58% while the BTA stat test had a sensitivity of 66% (p=0.233).

Table II. COMPARISON OF BTA stat TEST TO BARD BTA TEST

		BARD BTA TEST		
		POSITIVE	NEGATIVE	TOTAL
BTA stat TEST	POSITIVE	67	32	119
	NEGATIVE	20	42	62
	TOTAL	107	74	181

Table III presents the overall sensitivity in 220 patients with histologically confirmed bladder cancer recurrence (Table I), as well as the specificity in 107 patients who were being monitored for recurrence of bladder cancer and determined by cystoscopy and/or biopsy to have no evidence of disease (NED) at the time of the BTA stat determination.

Table III. BTA stat TEST RESULTS FROM PATIENTS WITH A HISTORY OF BLADDER CANCER

		BTA stat TEST		
		POSITIVE	NEGATIVE	TOTAL
HISTOLOGY/ CYSTOSCOPY RESULT	POSITIVE	147	73	220
	NEGATIVE	32	75	107
	TOTAL	179	148	327

Monitoring sensitivity = 67% (60 - 73, 95% confidence interval)
Monitoring specificity = 70% (61 - 79, 95% confidence interval)

Using the data in Table III and a 10%, 20%, and 30% hypothetical prevalence of bladder cancer recurrence, the positive predictive values and negative predictive values of the BTA stat test are presented in Table IV. Due to the possibility that bladder cancer may have been present in some of the NED individuals in this study, yet missed by cystoscopy, the true specificity in these patients and the positive and negative predictive values are likely to be higher.

Table IV. HYPOTHETICAL POSITIVE PREDICTIVE VALUES (PPV) AND NEGATIVE PREDICTIVE VALUES (NPV) OF THE BTA stat TEST

BLADDER CANCER RECURRENT PREVALENCE	PPV	NPV
10%	19.5	95.0
20%	35.5	89.4
30%	48.5	83.1

A subset of the patients with histologically confirmed bladder cancer (131) also had voided urine cytology (VUC) performed on the same sample as the BTA stat test (Table V). The BTA stat test was shown to be more sensitive than VUC in all categories except for Tis (tumor *in situ*).

Table V. BTA stat TEST AND VUC SENSITIVITIES

STAGE	N	SENSITIVITY BTA stat (%)	SENSITIVITY VUC (%)	SENSITIVITY BTA stat + VUC (%)
Ta	73	45	7	49
T1	27	85	41	85
≥T2	16	75	38	81
Tis	15	53	60	50

In a subset of patients (99) with a history of bladder cancer and no evidence of disease the specificity of the BTA stat test was 69% compared to VUC with a specificity of 97%.

CLINICAL SPECIFICITY

BTA stat test specificity (Table VI) was determined using urine samples from 555 individuals with no history of bladder cancer. Samples were collected from 5 different geographic locations throughout the United States and stored frozen (-80°C) until tested. Testing of samples for this study was performed at Bard Diagnostic Sciences, Inc. The average age was 55 years, 52% were female, 86% were caucasian, 5% African American, 4% Asian, Hispanic or other, and 3% of unknown ethnicity. The normal healthy population consisted of 80% non-smokers. The non-genitourinary (GU) diseases and cancers (71% of samples provided by females) included diabetes, arthritis, lupus erythematosus and other collagen degenerative diseases, as well as leukemia, lymphomas, breast, lung and gastrointestinal cancers. The non-bladder genitourinary cancers category (88% of samples provided by males) consisted of prostate, renal cell, renal TCC, endometrial, ovarian and other GU carcinomas. The GU disease category (92% of samples provided by females) consisted of patients with benign prostatic hyperplasia (BPH), prostatitis, urethritis, renal stones and disease, urinary tract infections (UTI), incontinence, sexually transmitted diseases (STD) and other disorders.

The results indicated that in healthy individuals and individuals without GU diseases and malignancies, the BTA stat test negative rate was 95% and 96%, respectively. Positive BTA stat test results may occur in patients with renal disease such as stones and nephritis and patients with renal cancer including upper tract TCC. Expected results may vary depending on the patient population tested.

Table VI. BTA stat TEST SPECIFICITY RESULTS

PATIENT TYPE	NUMBER OF SUBJECTS	TEST NEGATIVE (%)
Healthy Subjects	167	95
Non-smokers	100	93
Smokers	67	97
Non-Genitourinary Benign Diseases and Cancers	105	93
Non-Genitourinary Benign Diseases	52	96
Non-Genitourinary Cancers	53	89
Genitourinary Diseases	152	72
BPH	26	88
Benign Renal Disease	32	50
Misc. GU Disease	94	76
UTI/cystitis	30	60
STD	24	79
Other	40	85
Genitourinary Cancers	77	73
Prostate Cancers	45	78
Renal Cancers	7	28
Renal TCC	1	0
Renal Cell Carcinoma	6	33
Other Cancers	25	76
Genitourinary Trauma	54	33
TOTAL ^a	555	NA
History of Bladder Cancer - No Evidence of Disease ^b	107	70

^a total of subjects with no history of bladder cancer

^b No evidence of disease confirmed by cystoscopy and/or biopsy; 78% of patients in this category were males.

PERFORMANCE CHARACTERISTICS

HIGH DOSE HOOK EFFECT

High dose hook (prozone) effect tests were conducted to determine if the BTA stat test is free from interference from high concentration positive patient samples. Results showed that there was no prozone effect up to 12,400 U/mL bladder tumor associated antigen in a patient's urine sample, which was the highest concentration available for testing.

REPRODUCIBILITY

Three lots of BTA stat devices were used for the reproducibility studies to determine day-to-day, reader-to-reader and lot-to-lot variability. These studies were conducted by testing 10 replicates of 4 blinded samples per day for 5 days using three independent readers for each lot of devices. Between laboratory reproducibility studies were conducted at three laboratories by testing 10 replicates of 4 blinded samples on one lot of BTA stat devices. All reproducibility studies showed nearly total agreement with the exception of samples near the limit of detection, which is to be expected for qualitative tests.

INTERFERING SUBSTANCES

Normal and TCC positive urine pools containing the substances listed below were tested in the BTA stat test.

Table VII. INTERFERING SUBSTANCES

SUBSTANCE	HIGHEST LEVEL TESTED WITH NO INTERFERENCE	LEVEL AT WHICH SUBSTANCE INTERFERED
Possible Urine Constituents		
Hemoglobin	100 mg/dL	No interference at MLT*
White Blood Cells	10 ⁶ cells/mL	No interference at MLT
Red Blood Cells	10 ⁶ cells/mL	No interference at MLT
Albumin	1 g/dL	No interference at MLT
Bilirubin (unconjugated)	0.4 mg/dL	0.8 mg/dL ^A
IgG	10 mg/dL	No interference at MLT
Uric Acid	250 mg/dL	No interference at MLT
Ascorbic Acid	5 g/dL	No interference at MLT
Caffeine	58.3 mg/dL	117 mg/dL ^A
Nicotine	14 mg/dL	28 mg/dL ^A
Sodium chloride	368 mg/dL	730 mg/dL ^A
Ethanol	1% (v/v)	No interference at MLT
Possible Microbial Contaminants		
<i>Candida albicans</i>	1.25 x 10 ⁸ CFU/mL	2.5 x 10 ⁸ CFU/mL ^B
<i>Escherichia coli</i>	2.5 x 10 ⁸ CFU/mL	No interference at MLT ^C
<i>Pseudomonas aeruginosa</i>	2.5 x 10 ⁸ CFU/mL	No interference at MLT ^C
Therapeutic Agents		
Ampicillin	600 mg/dL	No interference at MLT
Acetaminophen	520 mg/dL	5.2 g/dL ^A
Acetyl Salicylic Acid	520 mg/dL	5.2 g/dL ^A
Doxorubicin-HCl	10 mg/dL	No interference at MLT
Mitomycin C	10 mg/dL	No interference at MLT
Nitrofurantoin	50 mg/dL	No interference at MLT
Phenazopyridine-HCl	80 mg/dL	100 mg/dL ^A
Thiotapa	10 mg/dL	No interference at MLT
Trimethoprim	50 mg/dL	No interference at MLT
Bacillus Calmette Guerin	20 mg/dL	No interference at MLT
Finasteride	2.5 mg/dL	No interference at MLT
Flutamide	100 mg/dL	No interference at MLT
Ioversol, 74% (imaging contrast agent)	1%	5% ^A
Urised	17.5 mg/dL	35 mg/dL ^D

* MLT - maximum level tested

^A Negative interference: substance decreased the intensity of a TCC positive urine test result

^B Subjecting samples to one freeze/thaw cycle resulted in no interference at 1.25 x 10⁸ CFU/mL, the MLT.

^C Results of interference studies unchanged by subjecting samples to one freeze/thaw cycle

^D Substance's coloration caused results for both normal and TCC positive urine to be difficult to interpret

In conclusion, the Bard BTA stat Test is substantially equivalent to the predicate device referenced in this submission.