Summary of Safety and Effectiveness Data

I. GENERAL INFORMATION

Device Generic Name:	Prostate Specific Antigen (PSA) Chemiluminescent Enzyme Immunoassay
Device Trade Name:	IMMULITE® PSA IMMULITE® 2000 PSA IMMULITE® Third Generation PSA IMMULITE®2000 Third Generation PSA
Applicant's Name and Address:	Diagnostic Products Corporation (DPC) 5700 West 96th Street Los Angeles, California 90045
Premarket Approval Application (PMA) Number:	P930027/S4
Date of Panel Recommendation:	Not applicable (see section X)
Date of Notice of Approval to the Applicant:	June 19, 2001

II. INDICATIONS FOR USE

The IMMULITE® PSA is indicated for in vitro diagnostic use with the Immulite Analyzer-for the quantitative measurement of prostate - specific antigen (PSA) in human serum, as an aid in the detection of prostate cancer when used in conjunction with digital rectal examination (DRE) in men aged 50 years or older.

IMMULITE® Third Generation PSA is indicated for in vitro diagnostic use with the Immulite Analyzer-for the quantitative measurement of prostate-specific antigen (PSA) in human serum, as an aid in the detection of prostate cancer when used in conjunction with digital rectal examination (DRE) in men aged 50 years or older.

IMMULITE® 2000 PSA is indicated for in vitro diagnostic use with the Immulite 2000 Analyzer- for the quantitative measurement of prostate - specific antigen (PSA) in human serum, as an aid in the detection of prostate cancer when used in conjunction with digital examination (DRE) in men aged 50 years or older. IMMULITE® 2000 Third Generation PSA is indicated for in vitro diagnostic use with the Immulite 2000 Analyzer-for the quantitative measurement of prostate specific-antigen (PSA) in human serum as an aid in the detection of prostate cancer when used in conjunction with digital rectal examination (DRE) in men aged 50 years or older.

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The IMMULITE® PSA, IMMULITE® Third Generation PSA, IMMULITE® 2000 PSA, and IMMULITE® 2000 Third Generation PSA were previously cleared or approved for marketing as an adjunctive test to aid in the management of prostate cancer patients (P930027/S1, K972095, K972021, and K974842/S1).

III. CONTRAINDICATIONS

There are no contraindications for the Immulite PSA, Immulite Third generation PSA, Immulite 2000 and Immulite 2000 Third Generation PSA.

IV. WARNINGS AND PRECAUTIONS

Refer to the device labeling for a list of the warnings and precautions.

V. DESCRIPTION OF DEVICES

IMMULITE PSA is a solid-phase, two-site chemiluminescent enzyme immunoassay for use with the Immulite Analyzer. The solid phase, a polystyrene bead enclosed within an IMMULITE Test Unit, is coated with a polyclonal antibody specific for PSA. The patient sample and reagent (containing alkaline phosphatase-conjugated monoclonal antibody) are incubated for approximately 30 minutes at 37°C in the Test Unit with intermittent agitation. During this time, PSA in the sample becomes bound to the surface of the bead. Unbound conjugate is removed by a centrifugal wash. The substrate is then added and the Test Unit is incubated for a further 10 minutes.

The chemiluminescent substrate, a phosphate ester of adamantyl dioxetane, undergoes hydrolysis in the presence of alkaline phosphatase to yield an unstable intermediate. The continuous production of this intermediate results in the sustained emission of light. The bound complex, and thus also the photon output as measured by the luminometer, is proportional to the concentration of PSA in the sample. The concentration of PSA in the patient sample is obtained using a stored master curve within the IMMULITE analyzer. The IMMULITE PSA assay has a reportable range of 0.04 to 150 nanograms of PSA per milliliter.

IMMULITE Third Generation PSA is a solid phase, two-site sequential chemiluminescent enzyme immunoassay for use with the Immulite Analyzer. The solid phase, a polystyrene bead enclosed within an IMMULITE Test Unit, is coated with a monoclonal antibody specific for PSA. The patient sample and a buffer/serum matrix are simultaneously introduced to the Test Unit and incubated for approximately 30 minutes at 37°C with intermittent agitation. During this time, PSA in the sample becomes bound to the surface of the bead. Unbound serum is then removed by a centrifugal wash. An alkaline phosphatase-conjugated polyclonal antibody is introduced, and the Test Unit is incubated for another 30-minute cycle. The unbound enzyme conjugate is removed by a

centrifugal wash. Substrate is then added and the Test Unit is incubated for a further 10 minutes.

The chemiluminescent substrate, a phosphate ester of adamantyl dioxetane, undergoes hydrolysis in the presence of alkaline phosphatase to yield an unstable intermediate. The continuous production of this intermediate results in the sustained emission of light. The bound complex, and thus also the photon output as measured by the luminometer, is proportional to the concentration of PSA in the sample. The concentration of PSA in the patient sample is obtained using a stored master calibration curve within the IMMULITE analyzer. The IMMULITE Third Generation PSA assay has a reportable range of 0.01 to 20 nanograms of PSA per milliliter.

IMMULITE 2000 PSA is a solid-phase, two-site chemiluminescent enzyme immunoassay for use with the Immulite 2000 Analyzer. The solid phase, a polystyrene bead, is coated with a polyclonal antibody specific for PSA. While the patient serum sample and alkaline phosphatase-conjugated monoclonal antibody are incubated for approximately 30 minutes at 37°C in the Reaction Tube with agitation, PSA in the sample is bound to form an antibody sandwich complex. Unbound conjugate is then removed by a centrifugal wash, after which substrate is added and the Reaction Tube is incubated at 37°C with agitation for a further 5 minutes.

The chemiluminescent substrate, a phosphate ester of adamantyl dioxetane, undergoes hydrolysis in the presence of alkaline phosphatase to yield an unstable intermediate. The continuous production of this intermediate results in the sustained emission of light. The bound complex, and thus also the photon output as measured by the luminometer, is proportional to the concentration of PSA in the sample. The IMMULITE 2000 PSA assay has a reportable range of 0.04 to 150 nanograms of PSA per milliliter.

IMMULITE 2000 Third Generation PSA is a solid-phase, two-site sequential chemiluminescent enzyme immunoassay for use with the Immulite 2000 Analyzer. The solid phase is a polystyrene bead coated with a monoclonal antibody specific for PSA. The patient sample and a buffer/serum matrix are introduced into the Reaction Tube containing the bead and incubated for approximately 30 minutes at 37°C with agitation. During this time, PSA in the sample binds to the monocolonal anti-PSA antibody-coated bead. Unbound serum is then removed by centrifugal wash.

An alkaline phosphatase -labeled polyclonal goat anti-PSA antibody is introduced, and the Reaction Tube is incubated for another 30-minute cycle. The unbound enzyme conjugate is then removed by a centrifugal wash. Substrate is then added, and the Reaction Tube is incubated for a further 5 minutes.

The chemiluminescent substrate, a phosphate ester of adamantyl dioxetane,

undergoes hydrolysis in the presence of alkaline phosphatase to yield an unstable intermediate. The continuous production of this intermediate results in the sustained emission of light. The bound complex, and thus also the photon output as measured by the luminometer, is proportional to the concentration of PSA in the sample. The IMMULITE 2000 Third Generation PSA assay has a reportable range of 0.01 to 20 nanograms of PSA per milliliter.

VI. ALTERNATIVE PRACTICES OR PROCEDURES

Alternative practices and procedures to aid in the detection of prostate cancer include a physical examination by digital rectal examination and imaging by ultrasound. Other devices for which there is an approved PMA for measuring serum total PSA are available to aid in the detection of prostate cancer in conjunction with DRE in men age 50 years or older. Confirmation of prostate cancer requires biopsy with histological examination of prostatic tissue.

VII. MARKETING HISTORY

IMMULITE PSA has been marketed in 52 countries; IMMULITE Third Generation PSA has been marketed in 38 countries; IMMULITE 2000 PSA has been marketed in 31 countries; IMMULITE 2000 Third Generation PSA has been marketed in 21 countries. These assays were previously approved or cleared for marketing as an aid in the management of prostate cancer patients under P930027/S1, K972095, K972021, and K974842/S1.

None of these PSA assays have been withdrawn from marketing for any reason relating to the safety and effectiveness of the device.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Assessment of patient status must not be based entirely on PSA results. Elevation in PSA values occurs in patients with benign prostatic disorders. A falsely elevated result could lead to an unnecessary biopsy. Low concentrations are not always associated with absence of disease. A false low PSA result could deprive the patient of a biopsy and treatment. There are no significant adverse effects on health of patients when this device is used as indicated.

IX. SUMMARY OF STUDIES

Non-clinical studies

Non-clinical studies were submitted in P930027/S1, K972095, K972021, and K974842/S1 to support the indications for use – to aid in the management of prostate cancer patients. New non-clinical studies were not performed since the assays have been previously cleared for use in the management of patients with prostate cancer. The following table summarizes non-clinical performance of the assays.

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Table 1

	IMMULITE PSA	IMMULITE Third Generation PSA	IMMULITE 2000 PSA	IMMULITE 2000 Third Generation PSA
PSA Antibody	-polyclonal antibody coated to bead. -monoclonal antibody conjugated with alkaline phosphatase.	-monoclonal antibody coated to bead. -polyclonal antibody conjugated with alkaline phosphatase.	-polyclonal antibody coated to bead. -monoclonal antibody conjugated with alkaline phosphatase.	-monoclonal antibody coated to bead. -polyclonal antibody conjugated with alkaline phosphatase.
Sample Size	10 µL	50 µL	10 µL	50 µL
Working Range	0.04 to 150 ng/mL	0.01 to 20 ng/mL	0.04 to 150 ng/mL	0.01 to 20 ng/mL
Analytical Sensitivity	0.03 ng/mL	0.003 ng/mL	0.04 ng/mL	0.003 ng/mL
Precision (intra-assay)	CV range: 3.1-6.1%	CV range: 3.0-7.7%	CV range: 2.2-3.6%	CV range: 3.0-7.3%
Precision (inter-assay)	CV range: 4.7-9.3%	CV range: 3.5-19%	CV range: 3.7-5.0%	CV range: 3.9-11%
Specificity	no clinically significant crossreactivity	No clinically significant crossreactivity	no clinically significant crossreactivity	no clinically significant crossreactivity
Parallelism	%Observed/Expected range: 98-124%	%Observed/Expected range: 86-118%	%Observed/Expected range: 91-113%	%Observed/Expected range: 89-106%
Spiking Recovery	%Observed/Expected range: 86-102%	%Observed/Expected range: 90-109%	%Observed/Expected range: 91-108%	%Observed/Expected range: 90-106%
Effect of Bilirubin	no clinically significant effect	No clinically significant effect	no clinically significant effect	no clinically significant effect
Effect of Hemolysis	no clinically significant effect	No clinically significant effect	no clinically significant effect	no clinically significant effect
No "high dose hook" effect up to levels of:	20,000 ng/mL	90,000 ng/mL	22,500 ng/mL	112,000 ng/mL

All four devices/assays have the same indication for use. The major differences between the devices are in the antibody used to coat the bead, the antibody used in the conjugate, and the analyzer to be used.

Clinical studies

Studies at three separate sites assessed the safety and effectiveness of IMMULITE PSA, IMMULITE Third Generation PSA, IMMULITE 2000 PSA and IMMULITE 2000 Third Generation PSA for the indications for use. Two retrospective studies were conducted in the United States, one in the northwest and one in the south. The third study was a prospective study conducted in Chile. Retrospective samples meeting the inclusion/exclusion criteria were sequentially selected for entry from the specimen banks maintained at each clinical site.

Inclusion criteria:

1. males aged 50 years or older
2. no evidence of acute prostatitis or urinary tract infection at time of specimen collection
3. no personal history of prostate cancer prior to specimen collection
4. A DRE result no more than 6 months prior to specimen collection and no more than 1 month, and more than 1 week, after specimen collection
5. If PSA results are greater than 4.0 ng/ml and/or DRE results are suggestive of cancer, documentation of biopsy results should be provided
6. If biopsy results are positive for cancer, then clinical and/or pathological staging should be provided
7. Serum specimens should be stored at -70C for no more than 5 years

Exclusion criteria:

1. treatment of benign prostatic hyperplasia within the previous 4 weeks
2. prior transurethral resection of the prostate
3. treatment with medications that might alter the serum PSA concentration
4. needle biopsy within the previous 6 weeks
5. men with a life expectancy of less than 10-15 years
6. if possible, do not include men with hereditary or familial history of prostate cancer

Studies using the IMMULITE PSA were conducted at three clinical sites. A total of 3810 serum specimens were collected. For all subjects 91% Caucasians, 6% African Americans, 2% Asians, <1% others or with no ethnic information. For the four race categories shown below, there were different percentages at each site:

Table 2

Race category	Site	% of subjects
Caucasian	Southern US Northwest US Chile	62.8% 91.2% 10%
Black	Southern US Northwest US Chile	23.4% 1.7% unstated
Hispanic	Southern US Northwest US Chile	9.4% 1.5% 90%
Asian, Native American, and unknown race	Southern US Northwest US Chile	4.4% 5.6% 0%

The mean age of subjects was 62.0 years.

To summarize the site analysis of patient characteristics, the following were found:

- cancer rate by site is not different ($p = 0.12$, cancer yield overall = 0.322)
- rate of elevated PSA ($p = 0.005$, Chi square test) and mean PSA ($p < 0.001$ by analysis of variance) by site are different
- rate of abnormal DRE by site is different ($p < 0.001$, Chi square test)
- race category by site is different ($p < 0.0001$, Chi square test)
- mean age by site is different ($p < 0.0001$ by analysis of variance)

To examine the percentage of subjects who had a biopsy at each site for differences from the overall percentage, the following table summarizes the results.

Table 3 Frequency of biopsy follow-up by clinical site

Site	Biopsied	non-biopsied	total	Frequency
Southwest US	37	964	1001	3.7%
Northwest US	52	425	477	10.9%
Chile	197	2135	2332	8.4%
Total	286	3524	3810	7.5%

The probability of equal frequencies of biopsy at each site was < 0.0001 (Chi square = 31.8 for 2 degrees of freedom).

Because there was a differential rate of biopsy, elevated PSA, and abnormal DRE at each site there could be differences in the performance of these diagnostic tests at each site. To investigate differences, several parameters were examined. The first test performance analyzed was the performance of PSA in relation to biopsy result. The odds ratio of cancer given an elevated PSA was calculated for each site and compared to the mean odds ratio. The mean odds ratio of cancer given an elevated PSA across the three sites was 2.67 (95% confidence interval 1.04 to 6.81). The odds ratio of cancer for all three sites was 1.85. The probability of homogeneous odds ratios was 0.78. There was no significant difference in odds ratios at each site compared to the mean odds ratio.

The next test performance analyzed was the performance of DRE in relation to biopsy result. The odds ratio of cancer given an abnormal DRE was calculated for each site and compared to the mean odds ratio. The mean odds ratio of cancer given an abnormal DRE across the three sites was 2.095 (95% confidence interval 1.085 to 4.048). The odds ratio of cancer given an abnormal DRE for all three sites was 2.348. The probability of homogeneous odds ratios was 0.71.

The third test performance analyzed was the performance of PSA and DRE (when

both are positive) in relation to biopsy result. The odds ratio of cancer given an abnormal PSA and DRE result (i.e., when both are positive) was calculated for each site and compared to the mean odds ratio. The mean odds ratio of cancer given an abnormal result across the three sites was 3.172 (95% confidence interval 1.477 to 6.812). The odds ratio of cancer given an abnormal result for all three sites was 3.187. The probability of homogeneous odds ratios was 0.75.

The last test performance analyzed was the performance of PSA in relation to DRE result. The odds ratio of an elevated PSA given an abnormal DRE result was calculated for each site for all subjects (biopsied and non-biopsied) and compared to the mean odds ratio. The mean odds ratio of an elevated PSA given an abnormal DRE result across the three sites was 5.714 (95% confidence interval 3.998 to 8.167). The odds ratios for the sites ranged from 2.443 to 9.593. The odds ratio of an elevated PSA given an abnormal DRE result for all three sites was 5.549. The probability of homogeneous odds ratios was 0,012. There was a significant difference in odds ratios at each site compared to the mean odds ratio. This result suggests that an elevated PSA in relation to an abnormal DRE result was not equivalent at each site. The results suggest that the odds ratios were not homogeneous due to large variation in the odds ratios. This result is consistent with non-homogeneous rates of abnormal DRE and rates of elevated PSA among all subjects at each sites, as noted above.

In summary, three of four analyses of test performance at the sites indicate that PSA and DRE performed equivalently despite differences in several patients characteristics. The rate of elevated PSA and mean PSA, rate of abnormal DRE, mean age, and distribution of racial categories were different between sites. However, the cancer rate was not different by site. Though patient characteristics were different between sites, the test performance was on average not different between sites. This rationale would support the pooling of data, at least for the Immulite PSA assay. If it is assumed that the distribution of PSA results using the other assays is the same as the distribution of PSA results for the Immulite PSA then it could be assumed that data for the other PSA assay can be pooled. However, the differential rate of biopsy and mean age differences between sites could also be associated with diagnostic test performance in ways other than across clinical study site. The poolability analysis does not exclude the possibility of non-random association of diagnostic test performance with such factors as:

- undergoing a biopsy procedure based on age or a diagnostic test value near the cut-off;
- family history of prostate cancer;
- racial or ethnic background.

The poolability analysis indicated that PSA and DRE performed equivalently despite differences in several patient characteristics and biopsy follow-up. The analysis did not exclude the possibility of non-random association between diagnostic test result (PSA and/or DRE), age, and biopsy follow-up.

Study Results

The studies for IMMULITE PSA were conducted at three sites. Samples from 3810 men, aged 50 or older, were collected. Of the 3810 total subjects, 3438 patients also had DRE results. The percentage of subjects with abnormal DRE results was 4.6%. Of the 3438 screened subjects with DRE results, 252 subjects had a biopsy (7.3% of total screened) and 81 cancers were found (2.4% of all screened, 32.1% of biopsied subjects).

The following table (Table 4) gives the numbers of all screened subjects and subjects who underwent biopsy with both PSA results (classified as positive when >4 ng/mL or negative when ≤4 ng/mL) and DRE results (classified as positive when suspicious for cancer and negative when non-suspicious).

Table 4

	PSA+	PSA-
DRE+	n=64 (PSA median=7.1) 34 (53%) subjects underwent biopsy (PSA median=7.6)	n=93 (PSA median=1.3) 16 (17%) subjects underwent biopsy (PSA median=2.3)
DRE-	n=353 (PSA median=5.9) 191 (54%) subjects underwent biopsy (PSA median=6.0)	n=2,928 (PSA median=1.0) 11 (0.4%) subjects underwent biopsy (PSA median=3.4)

The biopsy results are presented in the following tables (Tables 5, 6):

Table 5
Biopsy positive

	PSA +	PSA –	N
DRE+	19	5	24
DRE –	55	2	57
	74	7	81

Table 6
Biopsy Negative

	PSA +	PSA –	N
DRE +	15	11	26
DRE –	136	9	145
	151	20	171

Unbiased estimates of TP (sensitivity) and FP (1- specificity) can be obtained if the biopsy was performed on all subjects for whom DRE and PSA tests have been applied. But in these studies, subjects with both DRE and PSA negative test results were not verified by biopsy and, therefore, the TP and FP fractions of DRE and PSA cannot be calculated directly from these data. These data provide information about the ratio of TP relative to TP of DRE, ratio of FP to FP of DRE (see reference 3), and the rates of positive biopsy results (see reference 4).

It can be seen from Table 5 that the TP rates of DRE alone, PSA alone, the combination of PSA and DRE (when both are positive), and combination of DRE and/or PSA are as follows: TP(DRE) = 24/n1; TP(PSA) = 74/n1; TP(PSA and DRE) = 19/n1; TP(PSA and/or DRE) = 79/n1, where n1 is unknown number. Then the ratio of TP rates relative to DRE alone is unbiased:

TP(PSA)/TP(DRE)= 74/24= 3.1 with 95% CI: 2.2 - 4.4;
TP(PSA and DRE)/TP(DRE) = 19/24 = 0.79 with 95% CI: 0.74-0.84); and
TP(PSA and/or DRE)/TP(DRE)=79/24 = 3.3 with 95% CI: 2.4 - 4.6.

Similarly, the ratio of FP rates relative to the FP rate of DRE alone is calculated from Table 6: FP(DRE) = 26/n2; FP(PSA) = 151/n1; FP(PSA and DRE) = 15/n2; FP(PSA and/or DRE) = 162/n2 where n2 is unknown number. Then the ratio of FP rates relative to DRE alone is:

FP(PSA)/FP(DRE)=151/26=5.8 and
FP(PSA and DRE)/FP(DRE) = 15/26= 0.58 and
FP(PSA and/or DRE)/TP(DRE)=7162/26=6.2.

The study demonstrated that PSA determinations detected 68% (55/81) of cancers that DRE did not; PSA elevations greater than 4 ng/mL may warrant additional testing even if the DRE is negative. However, the converse is also true: a subject with suspicious DRE and a normal PSA may also require additional testing since DRE detected 6% (5/81) of cancers that PSA determinations did not. PSA alone detected 3.1 times more cancers than DRE alone while obtaining 5.8 times more false positive results. The combination PSA and/or DRE detected 3.3 times more cancers than DRE alone while obtaining 6.2 times more false positive results.

The following table (Table 7) gives the estimates of % positive biopsies in various diagnostic categories:

Table 7

	No. Of Subjects	No. of Biopsies (%)	No. of Prostate Cancers	% Positive Biopsies (95% CI)
All subjects	3438	252	81	32.1% (26.4% - 38.2%)
PSA > 4.0	417	225	74	32.9% (26.8%-62.6%)
DRE +	157	50	24	48.0% (33.6% - 62.6%)
PSA > 4.0 DRE+	64	34	19	55.9% (37.9% - 72.8%
PSA<= 4.0 DRE+	93	16	5	31.3% (13.2% - 57.1%
PSA > 4.0 DRE -	353	191	55	28.8% (22.5% - 35.5%)
PSA <= 4.0 DRE -	2928	11	2	18.2% (2.3% - 51.8%)

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One common difficulty of clinical studies of diagnostic tests is the potential for overestimated or underestimated test performance due to selection of a non-random subset of subjects with biopsy results from among all subjects. An absence for some reason of biopsy results for subjects who should have biopsy according to the study protocol but did not have biopsy can be considered as a problem of missing data. If the mechanism for the missing values is independent of the result of PSA test - then the estimation of the PSA performance will be unbiased but less efficient. All estimates (ratio of TP to TP (DRE), ratio of FP to FP (DRE),and the %positive biopsies for different diagnostic categories) are unbiased only if the missing results of biopsy occurred completely at random and in the same proportion for all groups (PSA+, DRE+), (PSA+, DRE-), and (PSA-, DRE+).

Statistical analysis showed that missing results of biopsy occurred at random only in two groups of subjects: (PSA+, DRE+ and PSA+, DRE-). Comparison of median PSA results suggests that the median PSA value for biopsied subjects with PSA > 4.0 ng/ml and abnormal DRE (7.6 ng/ml) is similar to the median PSA value for all screened subjects with these diagnostic test results (7.1 ng/ml). Comparison of median PSA results for biopsied subjects with PSA > 4.0 ng/ml and normal DRE (6.0 ng/ml) is similar to median PSA value for screened subjects with PSA > 4.0 ng/ml and normal DRE (5.9 ng/ml). Also, the proportion of biopsied subjects in these two cells are almost the same (53-54%).

Logistic regression analysis showed that the absolute value of the PSA assay was a significant predictor for data missingness in the cell (PSA-, DRE+). It indicated that biopsied subjects were not randomly selected from all screened subjects with abnormal DRE and PSA<4.0 ng/ml. Comparison of median PSA values for biopsied subjects with PSA < 4 ng/ml and abnormal DRE (2.3 ng/ml) is different from median values for screened subjects with these test results (1.3 ng/ml). Also the proportion of biopsied subjects in this group (17%) is much smaller than in PSA+, DRE+ and PSA+, DRE- groups. Subjects with negative results on both PSA and DRE were biopsied at a very low frequency (0.4%) and not at random. The median values for biopsied subjects with PSA < 4.0 ng/ml and normal DRE (3.4 ng/ml) is different from screened subjects with these test results (1.0 ng/ml). As a result of the lack of random selection to biopsy, initial estimators of ratio of TP rates relative to TP(DRE), ratio of FP rates relative to FP(DRE), and %positive biopsies were inaccurate estimates.

The missing data and subsequent overestimation of DRE performance stimulated statistical modeling (multiple imputation technique) in the subject counts for biopsy positive and biopsy negative subjects with abnormal DRE and PSA < 4.0 ng/ml (see reference 1). If initial subject counts are sufficiently large to allow building of a model, then the technique of multiple imputation for missing data can be applied. For the Immulite PSA study, the variables Age, PSA and the interaction term Age*PSA are significant predictors for the biopsy results for the subjects with PSA- DRE+ results. The multiple imputation technique estimated

8 subjects with positive biopsy results and 42 subjects with negative biopsy results (percentage of subjects with biopsy = 53.7% (50/93)). No modeling was performed for subjects with normal DRE and PSA < 4.0 ng/ml due to insufficient number of biopsied subjects (11) to allow estimation by modeling. After application of multiple imputation technique, the tables of the biopsy results adjusted for missingness are the following (Tables 8 and 9):

Subject count after statistical modeling

Table 8

Biopsy positive

	PSA+	PSA-
DRE+	19	8
DRE-	55	n/a

Table 9

Biopsy Negative

	PSA+	PSA-
DRE+	15	42
DRE-	136	n/a

The following table (Table 10) summarizes the subject counts by biopsy result prior to and after statistical modeling and the percent positive biopsies (positive predictive values):

Table 10

	No. Cancers without modeling	No. Cancers with modeling	No. Benign without modeling	No. Benign with modeling	%positive biopsies without modeling	% positive biopsies with modeling
PSA > 4.0	74	74	151	151	32.9% (26.8 -62.6)	32.9% (26.8 - 39.0)
DRE +	24	27	26	57	48.0% (33.6 - 62.6)	32.1% (22.2 - 42.1)
PSA > 4.0 DRE+	19	19	15	15	55.9% (37.9 - 72.8)	55.9% (39.2 - 72.6)
PSA<= 4.0 DRE+	5	8	11	42	31.3% (13.2 - 57.1)	16.0% (5.8 - 26.2)
PSA > 4.0 DRE -	55	55	136	136	28.8% (22.5 - 35.5)	26.7% (22.4 - 35.2)

The yield of cancer after modeling was 28.8% (95% confidence interval 23.5% to 34.0%). This yield is equivalent with the cancer yield prior to modeling (32.2%, 95% confidence interval 26.8% to 37.6%). The positive predictive value of DRE alone was 32.1% after modeling (negative predictive value 72.6% ± 3.1%). The positive predictive value of PSA alone was 32.9% after modeling (negative predictive value 86.7% ± 4.4%). At a cutoff of 4.0 ng/ml the Immulite PSA assay detects 91% of all cancer cases regardless of the result of the rectal examination. At a cutoff of 4.0 ng/ml, 26% of all benign cases regardless of the result of the rectal examination are less than 4.0 ng/ml in the Immulite PSA assay. The mean PSA in cancer subjects was 13.0 ng/ml ± 20.4. The mean PSA in subjects with benign disease was 6.6 ng/ml ± 4.6. The probability of no difference in the mean PSA value of cancer subjects compared with the mean PSA value of benign subjects was 0.001 (Mann Whitney test).

The positive predictive value of PSA and DRE (when both are positive) was 55.9% after modeling (negative predictive value 74.9% ± 2.7%). The positive predictive value of PSA and DRE is significantly higher than the modeled and

unmodeled cancer yield ($p < 0.01$). This result supports a conclusion that PSA and DRE in combination were able to detect cancer. The positive predictive value of PSA and DRE in combination is also significantly higher than the positive predictive value of DRE alone ($p = 0.01$). This supports a conclusion that PSA and DRE in combination detect more cancers than DRE alone.

The positive predictive value of PSA and/or DRE (when both PSA > 4.0 and abnormal DRE or PSA > 4.0 ng/ml alone or abnormal DRE alone) was 29.8% ± 2.8% after modeling (negative predictive value 100% ± 0%). This result supports a conclusion that PSA and DRE in conjunction were able to detect cancer.

The following table (Table 11) summarizes ratios of true positive and false positive rates prior to and after multiple imputation:

Table 11

	TP / TP(DRE) without modeling	FP / FP(DRE) without modeling	TP / TP(DRE) with modeling (95% CI)	FP / FP(DRE) with modeling (95% CI)
PSA	3.1	5.8	2.7 (1.9-3.9)	2.6 (2.0-3.5)
PSA and/or DRE	3.3	6.2	3.0 (2.0-3.5)	3.4 (2.7-4.2)
PSA and DRE	0.79	0.58	0.70 (0.66-0.75)	0.26 (0.25-0.28)

The data in the table indicate that the use of PSA increased true positive and false positive rates almost in the same proportion (TP/FP rate = 0.88 to 1.04) compared to DRE alone. The use of PSA and DRE (when both are positive) decreased the true positive rate and decreased the false positive rate relative to the rate for DRE but in a different proportion. The ratio of the true positive rate to the false positive rate for the combination of PSA and DRE (when both are positive) was 2.7. The use of PSA and DRE when both are positive yields more true positive subjects than false positive subjects relative to the TP/FP ratio of DRE alone. The use of the PSA testing increased the negative predictive values while the positive predictive values compared to the DRE alone were similar after modeling to positive predictive values prior to modeling.

In the same studies, 2928 participants in the clinical study were identified as asymptomatic subjects. The following table contains the distribution of PSA values by age decade for asymptomatic subjects who had both a negative PSA and DRE test result and were unbiopsied as well as for those subjects who were negative for cancer on biopsy. There is no certainty that all of these subjects were indeed free of prostate disease. Therefore, these data should be interpreted with caution since it is questionable whether these subjects represent a truly normal population. Presently, there are no data proving that the use of age-specific reference ranges are safe or effective.

Table 12 - Immulite PSA distribution by age decade

Distribution of PSA Levels	N	PSA Median	PSA 95th %ile
All subjects	2928	1.00	3.30
50–59 age group	1338	0.93	3.00
60–69 age group	1144	1.20	3.40
≥70 age group	446	1.40	3.60

Consider these limits as *guidelines* only. Each laboratory should establish its own reference ranges.

The studies for **IMMULITE Third Generation PSA** were conducted at two U.S. clinical sites. Samples were collected from 1477 men, aged 50 or older. Of these, 78% were Caucasian; 16% were African American; 4% were Asian; <1% were other or provided no ethnic information. Of these 1477 men, 1468 also underwent DRE. Of these 1468 subjects, 88 were biopsied for elevated (> 4.0 ng/mL) PSA and/or suspicious DRE. Thirty-five cancers were found.

The following table gives the number of all screened subjects with both PSA results (classified as positive when >4 ng/mL or negative when ≤4 ng/mL) and DRE results (classified as positive when suspicious for cancer and negative when non-suspicious).

Table 13

	PSA+	PSA-
DRE+	n=35 (PSA median=6.7) 16 (47%) subjects underwent biopsy (PSA median=6.3)	n=71 (PSA median=1.3) 15 (21%) subjects underwent biopsy (PSA median=2.3)
DRE-	n=126 (PSA median=5.8) 48 (38%) subjects underwent biopsy (PSA median=6.2)	n=1,236 (PSA median=1.0) 9 (0.7%) subjects underwent biopsy (PSA median=3.4)

The biopsy results are presented in the following tables:

Table 14

Biopsy Positive

	PSA+	PSA-	n
DRE+	10	5	15
DRE-	18	2	20
	28	7	35

Table 15

Biopsy Negative

	PSA+	PSA-	n
DRE+	6	10	16
DRE-	30	7	37
	36	17	53

The following table presents the % positive biopsies using the Immulite 3rd generation PSA assay:

Table 16

	No. of Subjects N (% of total)	No. of Biopsies N (%)	No. of Cancers N	% Positive Biopsies (95% CI)
All Subjects	1468	88	35	**39.8%** 29.6% - 50.0%
PSA>4.0	161 (11.0%)	64 (39.8%)	28	**43.8%** (31.4 - 56.7)
DRE+	106 (7.2%)	31 (29.2%)	15	**48.4%** (31.0 - 66.9)
PSA>4.0 DRE+	35 (2.4%)	16 (45.7%)	10	**62.5%** (35.4 - 82.2)
PSA≤4.0 DRE+	71 (4.8%)	15 (21.1%)	5	**33.3%** (14.2 - 61.6)
PSA>4.0 DRE-	126 (8.6%)	48 (38.1%)	18	**37.5%** (24.0 - 52.6)
PSA≤4.0 DRE-	1,236 (84.2%)	9 (0.7%)	2	**22.2%** (2.8 - 60.0)

The results indicated that PSA determinations detected 51% (18/35) of cancers that DRE did not; and DRE detected 14% (5/35) of cancers that PSA determinations did not. PSA alone detected 1.9 (28/15=1.9 with 95%CI: 1.2-3.0) times more cancers than DRE alone and the combination of PSA and/or DRE detected 2.2 (33/15=2.2 with 95% CI: 1.5-3.2) times more cancers than DRE alone. The use of PSA alone increased false positive rate 2.3 (36/16) times relative to DRE and the use of the combination of PSA and/or DRE increased the false positive rate 2.9 (46/16) times relative to DRE. The use of PSA and DRE when both are positive detected 0.67 times (10/15=0.67 with 95% CI: 0.55-0.78) fewer cancers than DRE alone and 0.38 times (6/16= 0.38 with 95% CI: 0.27-0.48) fewer false positives than DRE alone. The combination of PSA and DRE detected 1.8 times as many true positives as false positives relative to TP/FP ratio of DRE.

Logistic regression analysis indicated that the absolute value of the PSA test was a significant predictor for the absence of biopsy results for subjects with DRE+ and PSA-. The PSA median of biopsied subjects was 2.3 while PSA median of all screened subjects was 1.3. Also, the proportion of missing biopsy results in this group is larger than in the groups DRE+, PSA+ and DRE-, PSA+. The correlation of the absolute value of the PSA test with the performance of a biopsy lead to overestimation of the DRE performance. After application of multiple imputation technique, the tables of the biopsy results adjusted for missingness are following:

Table 17
Biopsy positive

	PSA +	PSA –
DRE+	10	6
DRE –	22	n/a

Table 18
Biopsy Negative

	PSA +	PSA –
DRE +	6	27
DRE –	36	n/a

n/a – not available

The following table (Table 19) summarizes the subject counts by biopsy result prior to and after statistical modeling and the percent positive biopsies (positive predictive values):

Table 19

	No. Cancers without modeling	No. Cancers with modeling	No. Benign without modeling	No. Benign with modeling	%positive biopsies without modeling	%positive biopsies with modeling
PSA > 4.0	28	32	36	42	43.8% (31.4 – 56.7)	43.2% (31.8 – 55.3)
DRE +	15	16	16	33	48.4% (31.0 – 66.9)	32.6% (20.0 – 37.5)
PSA > 4.0 DRE+	10	10	6	6	62.5% (35.4 - 82.2)	62.5% (35.4 - 82.2)
PSA<= 4.0 DRE+	5	6	10	27	33.3% (14.2 – 61.6)	18.2% (7.0 – 35.5)
PSA > 4.0 DRE -	18	22	30	36	37.5% (24.0 – 52.6)	37.9% (25.5 – 51.6)

The yield of cancer after modeling was 33.0% (95% confidence interval 24.4% to 41.6%). This yield is equivalent with the cancer yield prior to modeling (39.8%, 95% confidence interval 31.6% to 50.0%).

The positive predictive value of PSA and DRE is significantly higher than the adjusted cancer yield ($p = 0.007$). The positive predictive value of PSA and DRE is also significantly higher than the positive predictive value of DRE alone ($p = 0.002$).

The following table summarizes ratios of true positive and false positive rates prior to and after multiple imputation:

Table 20

	TP / TP(DRE) without modeling	FP / FP(DRE) without modeling	TP / TP(DRE) with modeling (95% CI)	FP / FP(DRE) with modeling (95% CI)
PSA	1.9	2.3	2.0 (1.3-3.2)	1.3 (0.8-1.9)
PSA and/or DRE	2.2	2.9	2.4 (1.6-3.4)	2.1 (1.6-2.7)
PSA and DRE	0.67 (0.55-0.78))	0.38 (0.27-0.48)	0.63 (0.51-0.74)	0.18 (0.08-0.29)

The data in the table indicate that the use of PSA alone increased true positive and false positive rates almost in the same proportion compared to DRE alone. The use of PSA and/or DRE also increased the true positive and false positive rates in the same proportion compared to DRE alone. The use of PSA and DRE when both are positive decreased the true positive rate and false positive rate compared to DRE. However, the reduction of TP and FP rates was not in equal proportions (i.e., TP/FP $\approx$ 1.0) but was 3.4 (95% CI: 2.2-4.7) relative to DRE alone. The use of the PSA testing increased the negative predictive values while the positive predictive values compared to the DRE alone were similar after modeling to positive predictive values prior to modeling.

In the same studies, 1236 participants were identified as asymptomatic subjects in the clinical study. The following table contains the distribution of PSA values by age decade for asymptomatic subjects who had both a negative PSA and DRE and were unbiopsied as well as for those subjects who were negative for cancer on biopsy. There is no certainty that all of these subjects were indeed free of prostate disease. Therefore, these data should be interpreted with caution since it is questionable whether these subjects represent a truly normal population. There are presently no data proving that the use of age-specific reference ranges are safe or effective.

Table 21 - Immulite 3rd Generation
PSA distribution by age decade

Distribution of PSA Levels	n	PSA Median	PSA 95th %ile
All subjects	1236	0.98	3.28
50–59 age group	612	0.81	2.73
60–69 age group	458	1.11	3.45
≥70 age group	166	1.35	3.65

Consider these limits as *guidelines* only. Each laboratory should establish its own reference ranges.

The study for **IMMULITE 2000 PSA** and **IMMULITE 2000 Third Generation PSA** was conducted at one clinical site. Samples were collected from 477 men, aged 50 or older. Of these 477 subjects, 20 (4%) were Asian; 8 (2%) were African American; 440 (92%) were Caucasian; 7 (<1%) were other and 2 (<1%) provided no ethnic information. All patients also underwent DRE. Of these, 52 were biopsied for elevated (> 4.0 ng/mL) PSA and/or suspicious DRE. Eighteen cancers were found.

IMMULITE 2000 PSA

The following table gives the number of all screened subjects with both PSA results (classified as positive when >4 ng/mL or negative when ≤4 ng/mL) and DRE results (classified as positive when suspicious for cancer and negative when non-suspicious).

Table 22

	PSA+	PSA-
DRE+	n=23 12 (52%) subjects underwent biopsy	n=31 5 (16%) subjects underwent biopsy
DRE-	n=47 26 (55%) subjects underwent biopsy	n=376 9 (2.4%) subjects underwent biopsy

The biopsy results are presented in the following tables:

Table 23
Biopsy positive

	PSA +	PSA –	N
DRE+	6	2	8
DRE –	9	1	10
	15	3	18

Table 24
Biopsy Negative

	PSA +	PSA –	N
DRE +	6	3	9
DRE –	17	8	25
	23	11	34

PSA determinations detected 50% (9/18) of cancers that DRE did not; and DRE detected 11% (2/18) of cancers that PSA determinations did not. PSA alone detected 1.9 (15/8) times more cancers than DRE alone. The combination of PSA and/or DRE detected 2.1 (17/8) times more cancers than DRE alone. The combination of PSA and DRE when both are positive detected 0.75 (6/8) times as many cancers as DRE alone. The use of PSA alone increased the false positive rate 2.6 (23/9) times relative to the rate for DRE. Use of the combination of PSA and/or DRE increased the false positive rate 2.9 (26/9) times relative to the rate for DRE. The combination of PSA and DRE when both are positive increased the false positive rate 0.7 times (6/9) relative to the rate of DRE alone.

In the same study, 376 participants were identified as asymptomatic subjects. The following table contains the distribution of PSA values by age decade for asymptomatic subjects who had both a negative PSA and DRE and were unbiopsied as well as for those subjects who were negative for cancer biopsy. There is no certainty that all of these subjects were indeed free of prostate disease. Therefore, these data should be interpreted with caution since it is questionable whether these subjects represent a truly normal population. There are presently no data proving that the use of age-specific reference ranges are safe or effective.

Table 25 - Immulite 2000 PSA distribution by age decade

Distribution of PSA Levels	*n*	PSA Median	PSA 95th %ile
All subjects	376	0.78	2.98
50–59 age group	159	0.60	2.30
60–69 age group	143	0.91	2.84
≥70 age group	74	1.17	3.17

Consider these limits as *guidelines* only. Each laboratory should establish its own reference ranges.

IMMULITE 2000 Third Generation PSA

Table 26

	PSA+	PSA-
DRE+	n=25 13 (52%) subjects underwent biopsy	n=29 4 (14%) subjects underwent biopsy
DRE-	n=60 32 (55%) subjects underwent biopsy	n=363 3 (0.8%) subjects underwent biopsy

The biopsy results are presented in the following tables:

Table 27
Biopsy positive

	PSA +	PSA –	N
DRE+	7	1	8
DRE –	9	1	10
	16	2	18

Table 28
Biopsy Negative

	PSA +	PSA –	N
DRE +	6	3	9
DRE –	23	2	25
	29	5	34

PSA determinations detected 50% (9/18) of cancers that DRE did not; and DRE detected 6% (1/18) of cancers that PSA determinations did not. PSA alone detected 2.0 (16/8) times more cancers than DRE alone. The combination of PSA and/or DRE detected 2.1 (17/8) times more cancers than the DRE alone. The use of PSA alone increased the false positive rate 3.2 (29/9) times relative to the FP rate of DRE. Use of the combination of PSA and/or DRE increased the false positive rate 3.6 (32/9) times relative to the rate of DRE. The combination of PSA and DRE when both are positive detected 0.9 (7/8) times as many cancers as DRE alone but decreased the false positive rate 0.7 times the false positive rate of DRE alone.

In the same study, 363 participants were identified as asymptomatic subjects. The following table contains the distribution of PSA values by age decade for asymptomatic subjects who had both a negative PSA and DRE and were unbiopsied as well as for those subjects who were negative for cancer on biopsy.

There is no certainty that all of these subjects were indeed free of prostate disease. Therefore, these data should be interpreted with caution since it is questionable whether these subjects represent a truly normal population. There are presently no data proving that the use of age-specific reference ranges are safe or effective.

Table 29 - Immulite 2000 3rd generation PSA distribution by age decade

Distribution of PSA Levels	N	PSA Median	PSA 95th %ile
All subjects	363	1.02	3.20
50–59 age group	157	0.88	2.83
60–69 age group	137	1.12	3.15
≥70 age group	69	1.48	3.58

Consider these limits as *guidelines* only. Each laboratory should establish its own reference ranges.

The following table presents the model adjusted % positive biopsies for the IMMULITE PSA, IMMULITE Third Generation PSA, IMMULITE 2000 PSA, and IMMULITE Third Generation PSA:

Table- 30 Model adjusted % positive biopsies for each PSA assay

	IMMULITE PSA	IMMULITE Third Generation	IMMULITE 2000 PSA	IMMULITE 2000 Third Generation
PSA>4.0	32.9% (26.8 - 39.1)	43.2% (31.8 – 55.3)	39.5% (24.0 – 54.0)	35.6% (21.7 – 49.5)
DRE+	32.1% (22.2 –42.1)	32.6% (20.0 – 37.5)	47.1% (25.3 – 72.2)	47.1% (23.4 – 70.8)
PSA>4.0 DRE+	55.9% (39.2 – 72.6)	62.5% (35.4 – 82.2)	50.0% (23.6 – 76.4)	53.8% (26.8 – 80.8)
PSA≤4.0 DRE+	16.0% (5.8 – 26.2)	18.2% (7.0 – 35.5)	40.0% (0 – 82.9)	25.0% (0 – 67.5)
PSA>4.0 DRE-	26.7% (22.4 – 35.2)	37.9% (24.0 – 51.6)	34.6% (16.4 – 52.8)	28.1% (12.6 – 43.6)

Method Comparison Studies

All four PSA assays were compared using Deming regression analysis. Samples used were within the working range of the assays. The table below presents the results of the Deming regressions, with columns as Y-variable, and rows as X-variable.

Table 31 - Deming Regression analysis

		Immulite PSA	Immulite 2000 PSA	Immulite 3rd Generation PSA	Immulite 2000 3rd generation PSA
Immulite PSA	N		477	474	473
	Slope		0.94	0.99	1.08
	(95% CI)		(0.93 to 0.95	(0.98 to 1.00)	(1.07 to 1.10)
	Intercept		-0.11	0.05	0.06
	(95% CI)		(-0.15 to -0.07)	(0.02 to 0.09	(0.02 to 0.22
	Corr. Coeff.		0.992	0.993	0.991
Immulite 2000 PSA	N	477		474	473
	Slope	1.06		1.06	1.16
	(95% CI)	(1.05 to 1.08)		(1.05 to 1.08)	(1.14 to 1.17)
	Intercept	0.12		0.15	0.18
	(95% CI)	(0.08 to 0.16)		(0.11 to 0.20)	(0.14 to 0.23)
	Corr. Coeff.	0.992		0.988	0.990
Immulite 3rd Generation PSA	n	474	474		472
	slope	1.01	0.94		1.10
	(95% CI)	(1.00 to 1.03)	(0.93 to 0.96)		(1.09 to 1.11)
	Intercept	-0.06	-0.15		-0.00
	(95% CI)	(-0.09 to -0.02)	(-0.19 to -0.10)		(-0.05 to 0.05)
	Corr. Coeff.	0.993	0.988		0.990
Immulite 2000 3rd generation PSA	n	473	473	472	
	slope	0.92	0.86	0.91	
	(95% CI)	(0.91 to 0.94)	(0.85 to 0.87)	(0.90 to 0.92)	
	Intercept	-0.06	-0.16	0.00	
	(95% CI)	(-0.10 to -0.02	(-0.20 to -0.12)	(-0.04 to 0.04)	
	Corr. Coeff.	0.991	0.990	0.990	

The data suggest that the Immulite PSA and Immulite 2000 PSA assays differ statistically by 5-6% in PSA value. These two assays have similar reportable ranges and immunoassay design. The percentage coefficient of variation for inter-assay imprecision for these assays is 5-10% (see table in non-clinical studies section). It is likely that the statistical difference in these studies is not clinically relevant since the inter-assay imprecision is of similar size.

The data suggest that the Immulite 3rd Generation PSA and Immulite 2000 3rd Generation PSA assays differ by 10% in PSA value. These two assays also have similar reportable ranges and immunoassay design. The percentage coefficient of variation for inter-assay imprecision for these assays is 3.5 to 20% (see table in non-clinical studies section). It is likely that the statistical difference in these studies is not clinically relevant since the inter-assay imprecision is of similar size.

Summary of clinical studies

Retrospectively obtained serum samples from 3810 men aged 50 or older without acute prostatitis, urinary tract infection, or personal history of prostate cancer were obtained from 3 clinical sites (2 in the US and 1 foreign site). Results of digital rectal examination were available for 3438 subjects. Ninety-one percent of subjects were Caucasian, 2% Asian, 6% African Americans, <1% other ethnic category or no ethnic information. Mean age of subjects was 62 years. The percentage of subjects with elevated Immulite PSA results was 12.2%. The

percentage of subjects with abnormal DRE results was 4.6%. Of the 3438 screened subjects, 252 subjects had a biopsy (7.3% of total screened) and 81 cancers were found (2.4% of all screened, 32.1% of biopsied subjects).

The mean PSA value of cancer subjects using the Immulite PSA assay was significantly higher than the mean PSA value of benign subjects ($p = 0.001$). Initial positive predictive value estimates for DRE and PSA were imprecise due to non-random verification of clinical status on biopsy. In addition, statistical modeling to correct for missing data was performed to obtain better estimation of DRE diagnostic performance. After modeling and calculation of ratio of TP, FP rates and %positive biopsies (positive predictive values) for data using the Immulite PSA assay, the use of PSA increased true and false positive rates almost in the same proportion compared to the DRE alone. It means that the use of the PSA testing increased the negative predictive values while the positive predictive values stayed almost the same compared to the DRE alone. The positive predictive value of PSA using the Immulite PSA assay and DRE in combination is also significantly higher than the positive predictive value of DRE alone ($p = 0.01$). This supports a conclusion that Immulite PSA assay and DRE in combination detect more cancers than DRE alone. Immulite PSA assay determinations detected 68% of cancers that DRE did not; DRE detected 6% of cancers that PSA determinations did not. Positive predictive values for the Immulite PSA assay were similar to positive predictive values for the Immulite 3rd Generation PSA, Immulite 2000 PSA, and Immulite 2000 3rd Generation PSA assays. The 95th percentile values for each PSA assay are less than 4 ng/ml. The PSA values of each assay do not differ from each other in a clinically meaningful way.

X. CONCLUSIONS DRAWN FROM THE STUDIES

Safety

As a routine diagnostic test, the PSA assay involves removal of blood for testing purposes. The test, therefore, presents no more safety hazard than other tests where blood is removed from subjects.

Effectiveness

The current studies showed that the use of PSA increased true positive and false positive rates in cancer detection in the same proportion compared to the DRE alone. It means that the use of the PSA testing increased the negative predictive value while the positive predictive value stayed the same compared to the DRE alone.

The positive predictive value of PSA in combination with DRE (when positive on both) is also significantly higher than the positive predictive value of DRE alone. In earlier studies of prostate cancer, DRE has been shown effective in cancer detection and has served as a more traditional cancer detection method.

Benefit/Risk Analysis

An elevated level of serum PSA may not necessarily indicate the presence of prostate cancer (88% false positive subjects in the current studies). Subjects with falsely elevated PSA may have unnecessary biopsies. A low level of serum PSA does not necessarily indicate the absence of prostate cancer (9% false negative subjects in the current studies). Subjects with falsely negative PSA results may not have a necessary biopsy. The physician should utilize PSA test results in conjunction with DRE, the patient's overall clinical assessment, and other diagnostic tests such as TRUS. Therefore, assessment of patient status should not be based exclusively on a serum PSA result. The risk of falsely identifying cancer to the risk of missing actual cancer (false positive to false negative ratio) for PSA is approximately 5:1 (10.2:1 in the current studies).

Confirmation of prostate cancer can only be determined by prostatic biopsy. However, it is estimated that the percentage of subjects falsely identified as free of cancer using prostate tissue from six cores is approximately 25% on first sampling and declines to approximately 5% on repeat biopsy one year later. Therefore, the presence of elevated PSA may fail to detect prostate cancer on first biopsy sampling. Physicians and patients should keep in mind the risks of failure to detect cancer when a negative biopsy result (absence of cancer) is received.

It is reasonable to conclude that the benefits of use of the device for the target population outweigh the risk of illness or injury when used as indicated in accordance with the directions for use.

XI. PANEL RECOMMENDATION

In accordance with the provisions of section 515 (c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Immunology Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA supplement substantially duplicates information previously reviewed by this panel.

XII. CDRH DECISION

FDA issued an approval order on June 19, 2001

XIII. APPROVAL SPECIFICATIONS

Directions for use: See the labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, precautions and Adverse Events in the labeling.

Postapproval Requirements and Restrictions: See approval order

XIV. References

1. Rubin, D. 1987. Multiple imputation for nonresponse in surveys. John Wiley and Sons, Inc.
2. Begg C.B. and Greenes R.A. Assessment of diagnostic tests when disease verification is subjects to selection bias. *Biometrics* 1983, 39, 207-215.
3. Schatzkin A., Connor R.J., Taylor P.R., and Bunnag B. Comparing new and old screening tests when a reference procedure cannot be performed on all screeners. *American Journal of Epidemiology* 1987, vol.125, No.4, p.672-678.
4. Xiao-Hua Zhou. Effect of verification bias on positive and negative predictive values. *Statistics in Medicine* 1994, vol.13, 1737-1745.
5. Chock C., Irwing L., Berry G., and Glasziou P. Comparing dichotomous screening tests when individuals negative on both tests are not verified. *Journal of Clinical Epidemiology* 1997, vol.50, No. 11, p.1211-1217.
6. Xiao-Hua Zhou. Correcting for verification bias in studies of a diagnostic test's accuracy. *Statistical Methods in Medical Research* 1998, 7:337-353.