I. General Information

Device Generic name(s):	Immunoassay for the *in vitro* quantitative determination of prostate specific antigen in human serum and plasma
Device Trade name(s):	Elecsys® Total PSA Immunoassay Elecsys® Total PSA CalSet
Applicant's name and address	Roche Diagnostics Corporation 9115 Hague Road Indianapolis, IN 46256 USA
PMA number:	P990056
Date of Panel recommendation:	None
Dates of Good Manufacturing Practice Inspection	September 30, 1999 and July 18, 2000
Date of notice of approval to the applicant	NOV 2 2 2000

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II. Indications for Use

The Elecsys Total PSA Immunoassay, a quantitative in vitro diagnostic test for total prostate-specific antigen (tPSA) in human serum and plasma, is indicated for the measurement of total PSA in conjunction with digital rectal examination (DRE) as an aid in the detection of prostate cancer in men aged 50 years or older. Prostate biopsy is required for the diagnosis of prostate cancer. The test is further indicated for serial measurement of tPSA to aid in the management of cancer patients. The electrochemiluminescence immunoassay "ECLIA" is intended for use on the Roche Elecsys 1010 and 2010 immunoassay analyzers.

III. Contraindications, Warnings and Precautions

There are no known contraindications for the Elecsys® Total PSA Immunoassay.

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

IV. Background/Device Description

Total PSA devices are not indicated as the sole diagnostic tool to confirm the presence or absence of malignant prostate disease. Patients with confirmed prostate cancer may have total PSA serum levels within the normal range. Some patients with non-malignant diseases of the prostate, including benign prostatic hyperplasia (BPH), may have elevated serum total PSA levels. Therefore, serum PSA values should be used in conjunction with the information from a complete clinical evaluation including DRE or other diagnostic tests. Confirmation of prostate cancer can only be determined by prostatic biopsy.

Manipulations of the prostate including DRE, biopsy, and minimally invasive/invasive surgical procedures can cause transient and often large increases in serum total PSA levels. Therefore, blood samples for PSA measurement should be taken before performing these procedures. Additional blood testing should be delayed at least 2 weeks to allow serum PSA to return to original levels.

The concentration of PSA in a given specimen determined with assays from different manufacturers can vary due to differences in assay methodology and reagent specificity. The results reported by the laboratory to the physician must include the identity of the PSA assay used. Values obtained for both complexed and total PSA from different PSA assays cannot be used interchangeably.

The Elecsys® Total PSA Immunoassay system is used for the measurement of PSA in human serum and plasma on the Elecsys® 2010 and Elecsys® 1010 Immunoassay Analyzers. The reagent kit contains three reagents: the M (Streptavidin-coated microparticles), R1 (Anti-PSA-Ab~biotin), and R2 (Anti-PSA-Ab!$Ru(bpy)_3^{2+}$), which

are combined as a bundle of three reagent bottles and placed on the instrument as a single unit.

The Elecsys® Total PSA Immunoassay is a two monoclonal antibody sandwich assay that recognizes prostate-specific antigen and prostate-specific antigen-ACT on an equimolar basis. A biotinylated monoclonal PSA-specific antibody and a monoclonal PSA-specific antibody labeled with a ruthenium complex react with PSA to form a complex. After incubation and the addition of streptavidin-coated microparticles, the complex binds to the solid phase via interaction of biotin and streptavidin.

The reaction mixture is aspirated into the measuring cell where the microparticles are magnetically held on the surface of an electrode. Unbound substances are then removed. Application of a voltage to the electrode induces chemiluminescent emission, which is measured by a photomultiplier.

Results are determined by a calibration curve that is instrument-specific. A 2-point calibration and a master curve are supplied to the instrument via the reagent bar code.

V. Alternative Practices and Procedures

Alternative practices and procedures for aiding in the detection of prostate cancer include a digital rectal examination and ultrasound imaging. 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 aged 50 years and older.

VI. Marketing History

The Elecsys® Total PSA Immunoassay and Elecsys® Total PSA CalSet have been marketed in the United States for the *in vitro* quantitative determination of total PSA in human serum and plasma for serial measurement of total PSA to aid in the management of cancer patients since December 1998. The Elecsys® Total PSA Immunoassay and Elecsys® Total PSA CalSet have been marketed worldwide since June 1998. The device has not been withdrawn from marketing in any country for reasons relating to the safety and effectiveness of the device.

VII. Adverse Effects of the Device on Health

Elevations in PSA occur in patients with benign prostatic disorders. Low concentrations are not always associated with absence of disease. Assessment of patient status must not be based entirely on PSA results. Potential adverse effects are:

1. A falsely low result could lead to a medical decision depriving the patient of a diagnostically definitive biopsy and beneficial treatment.
2. A falsely elevated result could lead to a medical decision causing unnecessary biopsy.

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. The percentage of subjects falsely identified as free of cancer declines to approximately 5% on repeat biopsy 1 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.

VIII. Summary of Studies

Non-Clinical Studies

This PMA is only for a new (class III) intended use and does not involve any changes in the reagents. The analytical performance characteristics of the assay are presented in previously cleared 510(k) submissions for the class II intended uses (K982948 and K982949).

Clinical Studies

The objective of the clinical studies was to determine the safety and effectiveness of the device in conjunction with digital rectal examination (DRE) as an aid in the detection of prostate cancer in men 50 years of age or older. In support of the above objective, this study determined the following specific goals:

- The positive predictive value of DRE alone and DRE in conjunction with a PSA value, as measured by the device, in detecting prostate cancer.
- The association between the values of PSA, as measured by the device, and the probability of finding prostate cancer on sextant-core biopsy, in conjunction with DRE.
- The distribution of PSA values, as measured by the device, in a cohort of men diagnosed with prostate cancer, by prostate biopsy.
- The distribution of PSA values, as measured by the device, in a cohort of men diagnosed with benign prostatic diseases, by prostate biopsy.
- The distribution of PSA values, as measured by the device, in a cohort of healthy men.

Study Design – Normal Cohort

For the Normal Healthy Cohort, 384 evaluable prospective samples were collected from subjects without a history of prostatic disease and were free of symptoms of other

diseases under an IRB approved protocol with patient informed consent from five family practice physician sites and one sample broker. The sites participated by collecting patient information and sample, and shipping samples to central testing laboratories. Samples were analyzed for PSA using the Elecsys® Total PSA Immunoassay at the testing laboratory. All samples were tested on both the Elecsys® 1010 and 2010 Immunoassay Analyzers in accordance with the manufacturer's instructions.

Inclusion and Exclusion Criteria

Inclusion Criteria

Any male regardless of race who voluntarily gave a blood sample for this study who:

1. Was 50 years of age or older.
2. Had no history of prostatic disease.
3. Was free of the signs and symptoms of all other disease.
4. Understood and signed the consent form.

Exclusion criteria:

1. Was younger than 50 years of age.
2. Had a history of prostatic disease.
3. Had any active disease.

Study Data - Normal Healthy Cohort

The distribution of PSA results was measured in a cohort of 395 normal healthy males recruited from five family practice physician sites and one sample broker. All men had normal size prostate glands as determined by DRE at time of sample draw or self-reported DRE within 6 months of sample draw. The median ages across the sites ranged from 58 to 68 years of age. Of 377 men with verifiable race information, there were 367 Caucasians (97%), 7 African Americans (2%) and 3 men of other ethnic origins (1%). No racial information was available for 18 subjects (4.5%).

A one-way analysis of variance was performed to determine if the ages of subjects differed by source of sample. The analysis indicated significant differences in mean age ($p < 0.001$).

The table below presents the 95th percentile estimate (and confidence intervals) of total PSA values in normal men by age decade as measured by the device on the Elecsys® 1010 and 2010 Immunoassay Analyzers. There were no significant differences between the two analyzers.

95th percentile estimate and confidence intervals of Total PSA Values Determined on the Elecsys® 1010 and Elecsys® 2010 Analyzers for Normal Healthy Cohort by age decade

	1010 analyzer			2010 analyzer		
Age decade	Estimate	Lower bound	Upper bound	Estimate	Lower bound	Upper bound
50-59	3.75	2.70	5.51	3.89	2.91	5.54
60-69	5.18	3.96	7.39	5.40	3.78	7.74
70+	6.16	4.75	7.55	6.22	4.78	7.91

Study Design - Prospective Disease Cohort

Men aged 50 years or older were enrolled into a multi-center study. For the Prospective Disease Cohort, 1121 evaluable prospective samples were collected between September 8, 1998, and May 30, 1999, under an IRB approved protocol with patient informed consent from 36 community urological clinical practices or university related practices throughout the United States. These samples were obtained from men who had been referred to a urologist with symptoms that lead to an evaluation for prostate cancer. Each subject had not been treated for benign prostate disease within 90 days prior to the referral and was not taking any medications on the exclusion list. No subject had a history of an evaluation for prostate cancer prior to the referral. Each site participated by collecting patient information and samples and shipping samples to a central testing laboratory. Data included complete demographics and clinical history showing the absence of disease.

Inclusion and Exclusion Criteria

Inclusion Criteria

Any male, regardless of race, presenting to a practicing urologist with symptoms that could lead to an evaluation for prostate cancer, including a transrectal ultrasound (TRUS), who:

1. Was age 50 years or older.
2. Had no history of an evaluation for prostate cancer prior to the referral.
3. Had not been treated for benign prostate disease within 90 days prior to the referral and was not taking any medications on the exclusion list.
4. Had not had a DRE at least 5 days prior to blood sample.
5. Understood and signed the informed consent form.
6. Had medical records available for verification.
7. Gave a blood sample no more than 15 days prior to biopsy.

Exclusion criteria:

1. Had a prior history of benign prostatic disease that had been treated within 90 days of the referral.
2. Had prior history of or treatment for prostate cancer.
3. Was younger than 50 years of age.
4. Had undergone a DRE examination or other forms of prostate manipulation less than 5 days prior to the sample blood draw.

Study Data - Prospective Disease Cohort

A total of 1121 men 50 years of age or older were serially accrued to participate in the study. The mean age of the cohort was 66.4 years (95% CI =65.9 to 66.8). Forty-seven and one half percent (47.5%) of the samples were obtained from seven sites. All other sites each contributed less than 4.0% of the samples. Eighty-three percent (83%) of the cohort were Caucasian and 12% were of Black Non-Hispanic ethnic origin. The remaining 5% were of various ethnic origins. A majority of the cohort (79.4%) reported taking at least one medication on a daily basis. The most common medication reported was to control high blood pressure (antihypertensive) while aspirin was the most common non-prescription medication taken on a daily basis.

The malignancy rates ranged from 0% to 80%. The average malignancy rate across sites was 34.9%. Approximately 60% of the sites had a cancer rate of 25% to 40%. A chi-square analysis of the cancer rate by clinical site resulted in an exact p value of 0.005 for the Likelihood Ratio Statistic (63.09, DF=35) with a 95% confidence interval of 0.003 to 0.007. This result indicates that there are differences in the malignancy rates across sites.

The mean age of the cohort was 66.4 years (95% CI= 65.9 to 66.8). A One-way Analysis of Variance indicated that there were significant differences between the sites ($p<0.001$).

To test for differences in mean PSA value as measured by the device on the 1010 and 2010 analyzers by site, a one-way Analysis of Variance was performed. The results indicated significant differences were present ($p<0.001$). In a separate analysis across all sites, the mean PSA value for benign subjects (6.71 ng/ml ± 0.21 on Elecsys® 2010) compared to cancer subjects (17.5 ng/ml ± 3.2 on Elecsys® 2010) was different regardless of analyzer type. It would be expected that cancer subjects would have statistically higher mean PSA values than benign subjects. The mean PSA value does not appear to be different between DRE abnormal and normal subjects when controlling for biopsy result.

Each man received a rectal examination of the prostate within 30 days of the sample draw (but not within 5 days of draw). Results of these examinations were classified at the site into 4 categories: normal, abnormal, suspicious for cancer, and other. Physicians who

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graded the prostate gland on a scale or indicated abnormalities in the gland used the other category. The category of "other" is considered as a non-normal rectal examination result. Eighteen percent (18%) of the subjects had results suspicious for cancer. Fifty-three and one half percent (53.5%) had results suspicious for cancer, abnormal, or other. Forty-six and one half percent (46.5%) had no indication of a prostate abnormality.

Analysis of DRE result by site indicated significant differences. Two types of analysis were performed based on the categorization of the DRE result. DRE was categorized as 1, 2, 3, or 8 corresponding to normal, abnormal, abnormal-suspicious for cancer, or other respectively. The mean DRE result by site was compared across all sites by one-way analysis of variance. The probability of equal mean DRE result was less than 0.0001. In addition, a chi square analysis of homogeneity by site of the percentage of subjects with a DRE result of 1 was significant ($p < 0.0001$). A similar analysis was performed for DRE results of 2 and 3 with similar results. This analysis also suggests that the percentage of subjects with a particular DRE result (1, 2, or 3) was significantly different by site. The site differences are consistent with site differences in other parameters (cancer rate, age, PSA).

Poolability analysis

The previously presented data indicated differences by site in the cancer rate, mean age, mean PSA, and mean DRE category. All of these parameters suggest, at minimum, a difference in populations at each site. An analysis of performance of various diagnostic tests could be used to support pooling of data across sites, if the performance is homogeneous across sites. This would suggest that despite differences in subjects at the sites, the tests are performing equivalently.

Two parameters were chosen for purposes of poolability. For each parameter, the critical factor was the probability of homogeneity of Odds ratios for a given parameter. The two chosen parameters were the Odds of cancer given an abnormal DRE result and the Odds of elevated PSA given an abnormal DRE result.

In the first analysis, the Odds ratio of cancer given an abnormal DRE result was examined across sites. This parameter was in part chosen since DRE is an older method for detecting cancer that is easily performed in men aged 50 and older who could be screened for prostate cancer. Digital rectal examination is capable of detecting prostate cancer on its own (though with poorer performance than the combined use with PSA). No assumptions are made about the urologic characteristics of men being examined or the underlying cancer rate. The categorization of DRE result as abnormal included subjects with abnormal DRE, abnormal-suspicious for cancer, and other categories. The categorization of cancer was determined from the biopsy outcome. The results for each site were determined from the database in a series of 2 x 2 contingency tables of DRE result and biopsy result. The Odds ratio for cancer given an abnormal DRE result were calculated for each site. The Odds ratio for cancer given an abnormal DRE ranged from 0.105 to 19.00. The mean Odds ratio for all sites was 1.918 (95% CI=1.442 to 2.551). The probability of homogeneity was 0.85. Thus, this parameter suggests that all subjects

at all sites had equivalent odds of cancer given an abnormal DRE result despite the statistical difference in cancer rates and DRE results for subjects at all the sites.

In the second analysis, the Odds ratio for an elevated PSA given an abnormal DRE result was examined. This parameter was chosen since it represented a method of cancer detection directly related to the final performance of the device in conjunction with DRE. The categorization of DRE result as abnormal was based on DRE results of abnormal, abnormal-suspicious for cancer, or other. The categorization of elevated PSA was based on elevation above 4 ng/ml. The results for each site were determined in a series of 2 x 2 contingency tables of PSA result and DRE result. The Odds ratio for an elevated PSA given an abnormal DRE result was calculated for each site. The Odds ratio for an elevated PSA given an abnormal DRE ranged from 0.067 to 2.800. The mean Odds ratio for all sites was 0.505 (95% CI=0.368 to 0.692). The probability of homogeneity was 0.98. Thus this parameter suggests that all subjects at all sites had equivalent odds of an elevated PSA given an abnormal DRE result despite the statistical difference in mean PSA and mean DRE for subjects at the sites.

The analysis of two parameters across all sites suggests that there is homogeneity of diagnostic test results. This supports a conclusion that the data can be pooled.

Results for Prospective cohort

Combining PSA values across site give the information in Table 2.

Table 2. Distribution of PSA Values by Biopsy Result and Digital Rectal Examination Result for the Elecsys® 2010 and 1010 Analyzers

		Benign Prostate Biopsy			
DRE	**Analyzer**	**Count**	**Median**	**Minimum**	**Maximum**
Normal	2010	375	5.8	0.4	75.8
	1010	375	6.0	0.4	76.9
Abnormal	2010	355	4.9	0.3	29.6
	1010	355	5.1	0.3	33.2
Total	*2010*	*730*	*5.4*	*0.3*	*75.8*
	1010	*730*	*5.6*	*0.3*	*76.9*
		Malignant Prostate Biopsy			
DRE	**Analyzer**	**Count**	**Median**	**Minimum**	**Maximum**
Normal	2010	146	7.2	2.5	122.1
	1010	146	7.3	2.7	115.2
Abnormal	2010	245	7.8	0.5	778.5
	1010	245	8.0	0.5	801.0
Total	*2010*	*391*	*7.4*	*0.5*	*778.5*
	1010	*391*	*7.5*	*0.5*	*801.0*

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As shown in Table 3, within this cohort of 1121 males, 391 (34.9%) prostate cancers were detected by biopsy. Abnormal Digital Rectal Examination (DRE) results were reported for 245 (62.7%) of the 391 prostate cancers while PSA results above 4 ng/ml were reported for 342 (87.5%) and 336 (85.9%) cancers for the Elecsys® 1010 and 2010 Immunoassay Analyzers, respectively. If men are biopsied when they have an abnormal DRE result or a PSA value above 4.0 ng/ml, 96.9% (379/391) of the prostate cancer cases would be detected. This supports a conclusion that PSA identified 134 cancers that DRE reported as normal.

Table 3. Distribution of DRE and PSA Results for Prostate Cancers Detected by Biopsy in Men 50 Years or Older Referred to a Urologist for Prostate Evaluation

Elecsys® Analyzer	No. of Malignant Prostate Biopsies	DRE+*	PSA+**	PSA+ and DRE+	PSA+ and DRE-***	PSA+ or DRE+
2010	391 *(34.9%)*	245 *(62.7%)*	336 *(85.9%)*	202 *(51.7%)*	134 *(34.3%)*	379 *(96.9%)*
1010	391 *(34.9%)*	245 *(62.7%)*	342 *(87.5%)*	208 *(53.1%)*	134 *(34.3%)*	379 *(96.9%)*

* abnormal DRE
** PSA value $\geq$ 4 ng/ml
*** normal DRE

The average cancer prevalence was 0.349 ± 0.014. The following table summarizes various positive predictive values with a comparison value using the Elecsys® 2010 Immunoassay Analyzer:

Positive predictive value parameter	Value ± Se	Comparison	Probability of no difference
PSA and DRE	0.475 ± 0.024	Prevalence PPV (DRE only)	<0.0001 <0.0001
DRE	0.408 ± 0.020	Prevalence	<0.0001
PSA	0.390 ± 0.017	Prevalence	<0.0001
PSA and/or DRE	0.366 ± 0.015	Prevalence	<0.0001

For all parameters listed, there is a statistically significant result with the comparison value (prevalence or PPV of DRE). This would support a conclusion that PSA in conjunction with DRE can detect cancer better than the overall cancer prevalence.

Comparison of positive predictive values derived from the PSA test on the Elecsys® 2010 and 1010 are summarized below:

Parameter	PPV on 1010 analyzer	PPV on 2010 analyzer
PSA and DRE	0.471 ± 0.024	0.475 ± 0.024
PSA	0.386 ± 0.016	0.390 ± 0.017
PSA and/or DRE	0.363 ± 0.015	0.366 ± 0.015

Note that the positive predictive values of PSA and DRE, PSA, and PSA and/or DRE for each analyzer system are similar.

IX. Conclusions drawn from 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 positive predictive values for PSA alone and in combination with DRE (i.e. when both tests are positive) detects significantly more cancer cases than the overall cancer prevalence among biopsied subjects. 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 published studies of prostate cancer, DRE has been shown effective in cancer detection and has served as a more traditional cancer detection method. In the current studies, DRE also detected cancer significantly better than the overall cancer prevalence. The combination of PSA and DRE detected significantly more cancers than DRE detected as indicated by the higher positive predictive value for PSA and DRE compared to the predictive value for DRE alone.

The median PSA in subjects with cancer was 7.5 ng/ml. At a cutoff of 4.0 ng/ml the device detects 87% of all cancer cases regardless of the result of the rectal examination. The median PSA in subjects with benign disease was 5.5 ng/ml. At a cutoff of 4.0 ng/ml the device detects 27% of all benign cases regardless of the result of the rectal examination.

Ninety-five percent (95%) of normal men aged 50-59 have PSA values less than 3.9 ng/ml, 95% of men aged 60-69 have PSA values less than 5.4 ng/ml, and 95% of men aged 70 and over have PSA values less than 6.2 ng/ml.

Benefit/Risk Analysis

An elevated level of serum PSA may not necessarily indicate the presence of prostate cancer (73% 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 (14% 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.

Confirmation of prostate cancer can only be determined by prostatic biopsy. However, it is estimated, in the literature, that the percentage of subjects falsely identified as free of cancer using prostate tissue from six cores is approximately 25% on first sampling. The percentage of subjects falsely identified as free of cancer declines to approximately 5% on repeat biopsy 1 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.

X. 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 substantially duplicates information previously reviewed by this panel.

XI. CDRH Decision on Application

FDA issued an approval order on NOV 22 2000.

The applicant's manufacturing facilities were inspected on September 30, 1999, and July 18, 2000, and were found to be in compliance with the device Good Manufacturing Practice regulations.

XII. Approval Specifications

Directions for use: See the labeling.

Conditions of Approval: CDRH Approval of this PMA is subject to full compliance with the conditions described in the approval order.

Postapproval Requirements and Restrictions: See approval order.