

**510 (k) Summary of
Safety and Effectiveness**

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

Name: Diagnostic Products Corporation

Address: 5700 West 96th Street
Los Angeles, California 90045

Telephone Number: (310) 645-8200

Contact Person: Edward M. Levine, Ph.D.

Date of Preparation: September 16, 1998

Catalog Number: LKAP1, LKAP5 (100, 500 tests)
L2KAP2 (200 tests)

Device Name

Trade: IMMULITE® and IMMULITE® 2000 AFP

Common: Reagent system for the determination of AFP antigen in serum.

Classification: LOJ, Class II device

Manufacturer: Euro/DPC Limited
Glyn Rhonwy
Llanberis, Gwynedd LL55 4EL
United Kingdom
(Manufactured under a Quality System-ISO 9002/EN29002/BS 5750)

Sole U. S. Importer: Diagnostic Products Corporation (DPC)
5700 West 96th Street
Los Angeles, CA 90045-5597

Establishment Registration #: Euro/DPC – Not applicable
DPC Registration number is 2017183

Substantially Equivalent Predicate Device: Abbott IMx® AFP (P820060)

Description of Device:

IMMULITE® AFP is a clinical device for use with the IMMULITE Automated Immunoassay Analyzer. IMMULITE® 2000 AFP is a clinical device for use with the IMMULITE 2000 Automated Immunoassay Analyzer.

Intended Use of the Device:

IMMULITE AFP is for *in vitro* diagnostic use with the IMMULITE Analyzer – for the quantitative measurement of alpha-fetoprotein (AFP) in human serum, as an aid in the management of patients with nonseminomatous testicular cancer. IMMULITE 2000 AFP is for *in vitro* diagnostic use with the IMMULITE 2000 Analyzer – for the quantitative measurement of alpha-fetoprotein (AFP) in human serum, as an aid in the management of patients with nonseminomatous testicular cancer.

Summary and Explanation of the Test:

Alpha-fetoprotein (AFP) is a single-chain glycoprotein with a molecular mass of approximately 70,000 daltons. AFP shares considerable sequence homology with albumin, and is produced by the fetus primarily in cells of the yolk sac, gastrointestinal tract and liver. AFP appears as a major serum protein in the fetus, but its concentration decreases rapidly toward birth. The reappearance of elevated AFP concentrations in adult serum has been observed not only during pregnancy, but also in conjunction with several benign and malignant diseases.

Discovery of an embryo-specific protein, AFP, in human fetal serum was reported in 1956 by Bergstrand and Czar. In 1963, Abelev observed that transplanted mouse hepatocellular carcinomas were capable of synthesizing AFP and secreting it into the circulation. The first report of AFP as a human tumor-associated protein was made by Tatarinov in 1964, based on his observations of elevated AFP concentrations in patients with primary liver tumors. In 1968, subsequent to these discoveries, Masopust et al. reported the occurrence of elevated AFP concentrations in the serum of patients with teratocarcinomas of the testis.

Since the report by Masopust et al, elevated levels of AFP have been observed not only in patients with nonseminomatous testicular cancer, but also in patients with other malignancies such as hepatocellular carcinoma, ovarian cancer, gastrointestinal cancer and pulmonary cancer. Serum AFP is frequently elevated in benign hepatic conditions such as acute viral hepatitis, chronic active hepatitis and cirrhosis. Conditions of pregnancy, ataxia telangiectasia and hereditary tyrosinemia have also presented with elevated concentrations of AFP.

Seminomas, in pure form, do not present with elevated concentrations of AFP. However, elevated concentrations of serum AFP have been observed in patients diagnosed with seminomatous testicular cancer accompanied by nonseminomatous metastases. During

chemotherapy, patients with advanced seminoma and hepatic dysfunction have also presented with elevated serum AFP concentrations. The interpretation of elevated AFP concentrations in patients with seminoma requires special consideration and should assist the clinician in the selection of appropriate therapy.

The clinical utility of AFP measurement as an aid in the management of patients with nonseminomatous testicular cancer is well documented. AFP measurement has found clinical application as an aid in assessing the extent of disease. It has been observed that the frequency of AFP elevation increases with the stage of nonseminomatous testicular cancer.

Serial measurements of serum AFP have been shown to reflect the effectiveness of therapeutic regimens in patients with nonseminomatous testicular tumors. Post-surgical determinations of AFP are particularly valuable. The presence of residual tumor is strongly suggested if post-operative AFP concentrations fail to return to normal. The accurate interpretation of post-surgical changes in AFP concentration requires consideration of its metabolic decay rate. When utilizing AFP for monitoring therapy or disease recurrence during chemotherapy, it should be noted that levels often fall rapidly during chemotherapy, reaching normal levels while tumor masses are still evident. In such instances, completion of the planned therapy has been recommended.

Following therapy or surgery, serial measurements of AFP have also proved clinically useful when monitoring for progression or recurrence of disease in patients with nonseminomatous testicular cancer. It has been reported that AFP levels frequently rise during disease progression and fall during disease remission. Elevated AFP levels have frequently been observed to accompany tumor recurrence before progressive disease is clinically evident.

Performance Equivalence - Technology Comparison:

IMMULITE AFP is a solid-phase, two-site sequential chemiluminescent immunometric assay and Abbott IMx AFP is a microparticle enzyme immunoassay (MEIA). The technology in DPC's IMMULITE AFP is identical to technology used in previously cleared and commercially marketed IMMULITE products.

IMMULITE AFP is a solid-phase, two-site sequential chemiluminescent immunometric assay. The solid phase, a polystyrene bead enclosed within an IMMULITE Test Unit, is coated with a monoclonal antibody specific for AFP.

The patient sample and a buffer/serum matrix are simultaneously introduced into the Test Unit, and incubated for approximately 30 minutes at 37 °C with intermittent agitation. During this time, AFP in the sample binds to the monoclonal, anti-AFP antibody-coated bead. Unbound plasma is then removed by a centrifugal wash.

An alkaline phosphatase-labeled polyclonal anti-AFP 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, thus improving precision by providing a window for multiple readings. The bound complex - and thus the photon output, as measured by the luminometer - is proportional to the concentration of AFP in the sample.

IMMULITE 2000 AFP is a solid-phase, two-site chemiluminescent immunometric assay. The solid phase is a polystyrene bead coated with a monoclonal antibody specific for AFP.

The patient serum 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, AFP in the sample binds to the monoclonal, anti-AFP antibody-coated bead. Unbound plasma is then removed by a centrifugal wash.

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

The concentration of AFP in the sample is then measured in the same manner as that of IMMULITE AFP.

The **IMx AFP** assay is based on the Microparticle Enzyme Immunoassay (MEIA) Technology. The IMx AFP reagents and samples are added to the reaction cell in the following sequence:

- The probe/electrode assembly delivers the sample, Specimen Diluent and Anti-AFP Coated Microparticles to the incubation well of the reaction cell. During the incubation of this reaction mixture the AFP binds to the Anti-AFP Coated Microparticles forming an antibody-antigen complex.
- An aliquot of the reaction mixture is transferred to the glass fiber matrix. The microparticles bind irreversibly to the glass fiber matrix.
- The matrix is washed to remove unbound materials.
- Anti-AFP:Alkaline Phosphatase Conjugate is dispensed onto the matrix and binds to the antibody-antigen complex.
- The matrix is washed to remove unbound materials.

- The substrate, 4-Methylumbelliferyl Phosphate, is added to the matrix and the fluorescent product is measured by the MEIA optical assembly.

Performance Equivalence - Method Comparison

IMMULITE AFP

The IMMULITE AFP assay was compared to Abbott's IMx AFP, a commercially available EIA, at two clinical sites. A total of 264 specimens from male patients with nonseminomatous testicular cancer, malignant and nonmalignant conditions, and a few female patients, were evaluated in a clinical site in the northwestern United States. The qualitative comparison of the IMMULITE AFP and Abbott's IMx AFP values yielded the following results.

IMx AFP	IMMULITE AFP		Relative Sensitivity	Relative Specificity
	Positive*	Negative		
Positive*	74	4	94.9%	97.3%
Negative	5	181		

* IMMULITE AFP uses 5 IU/mL as the cutoff.

* IMx AFP uses 7.36 IU/mL (= 8.9 ng/mL) as the cutoff.

Agreement: 96.6%

95% Confidence Limits (by exact method) for Relative Sensitivity and Specificity, respectively:

87.4% - 98.6% and 93.8% - 99.1%

In a second study in the southern United States, a total of 213 specimens from male patients with seminomatous and nonseminomatous testicular cancer, patients with malignant conditions, plus a few females patients were tested with both IMMULITE AFP and Abbott's IMx AFP, with the following results.

IMx AFP	IMMULITE AFP		Relative Sensitivity	Relative Specificity
	Positive*	Negative		
Positive*	62	3	95.4%	97.3%
Negative	4	144		

* IMMULITE AFP uses 5 IU/mL as the cutoff.

* IMx AFP uses 7.36 IU/mL (= 8.9 ng/mL) as the cutoff.

Agreement: 96.7%

95% Confidence Limits (by exact method) for Relative Sensitivity and Specificity, respectively:

87.1-99.0% and 93.2% - 99.3%

The specimens from the two clinical sites with AFP measurements within the calibration ranges of both IMMULITE AFP and IMx AFP (n = 424) were compared in a linear regression, yielding the following relationship between the two assays in IU/mL.

$$\text{IMMULITE AFP} = 0.83 \times \text{IMx AFP} - 0.17 \quad r = 0.99$$

IMMULITE 2000 AFP

The assay was compared to DPC's IMMULITE AFP in a linear regression on a total of 205 samples from male patients in different clinical stages (pre and post surgery) of their nonseminomatous testicular cancer, with a concentration range of approximately 0.3 to 280 IU/mL.

$$\text{(IML 2000)} = 1.04 \text{ (IML)} + 0.34 \text{ IU/mL}$$

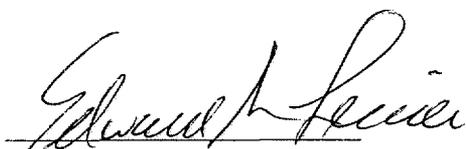
Means:

57 IU/mL (IMMULITE 2000) $r = 0.998$

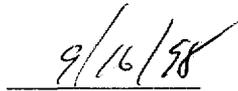
54 IU/mL (IMMULITE)

Conclusion:

The conclusions drawn from the clinical and nonclinical studies demonstrate that the device is safe and effective and performs as well as, or better than, the current legally marketed device.



Edward M. Levine, Ph.D.
Director, Clinical Affairs


Date



DEC 7 1998

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

Edward M. Levine, Ph.D.
Director, Clinical Affairs
DIAGNOSTIC PRODUCTS CORPORATION
5700 West 96th Street
Los Angeles, CA 90045

Re: K983263

Trade Name: IMMULITE® and IMMULITE® 2000 AFP
Regulatory Class: II
Product Code: LOJ
Dated: November 16, 1998
Received: November 17, 1998

Dear Dr. Levine:

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

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

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

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

Sincerely yours,

A handwritten signature in black ink that reads "Steven Gutman". The signature is written in a cursive style with a large initial 'S'.

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

Enclosure

510(k) Number (if known): K 983263

Device Name: IMMULITE® AFP

Indications For Use:

IMMULITE AFP is for *in vitro* diagnostic use with the IMMULITE Analyzer – for the quantitative measurement of alpha-fetoprotein (AFP) in serum, as an aid in the management of patients with nonseminomatous testicular cancer.

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

Concurrence of CDRH, Office of Device Evaluation (ODE)

Prescription Use
(Per 21 CFR 801.109)

OR

Over-The-Counter Use

(Optional Format 1-2-

