DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

JUL 25 1997

William R. Gilbert, Ph.D.
Manager, Scientific Affairs
Sigma Diagnostics
545 South Ewing Avenue
St. Louis, Missouri 63103

Re: K972144
ACCUCOLOR™ Antithrombin III(AT-III) Kit
Regulatory Class: II
Product Code: JBQ
Dated: June 3, 1997
Received: June 6, 1997

Dear Dr. Gilbert:

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 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 requirement, 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.

Under the Clinical Laboratory Improvement Amendments of 1988 (CLIA-88), this device may require a CLIA complexity categorization. To determine if it does, you should contact the Centers for Disease Control and Prevention (CDC) at (770) 488-7655.

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/dsmamain.html".

Sincerely yours,

Steven Gutman

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

JUL 25 1997

Summary of Safety and Effectiveness
Accucolor Antithrombin III Assay Kit (CRS117A) K972144

Antithrombin III (ATIII) is the major inhibitor of plasma thrombin and factor Xa. It is also an important inhibitor of activated factors IXA., XIa, and XIIa.[1] The inhibitory activity of ATIII towards thrombin is greatly increased (2-3 orders of magnitude) in the presence of heparin.

ATIII levels are decreased in immunological and functional tests in Type I, or genetic, ATIII deficiencies. Only functional levels are decreased in Type II ATIII deficiencies in which heparin enhancement does not proceed normally[2]. Acquired deficiency of ATIII may occur in consumptive coagulopathies (e.g. DVT, DIC, pulmonary emboli), other disease states (e.g. severe liver disease, nephrotic syndrome), surgery, pregnancy, minor trauma, and certain therapy courses such as L-asparaginase [1,3,4]. ATIII levels may be lower in infants (up to 6 months) slightly lower in women, and further decreased with increasing age.[5] Agents which have been reported to increase ATIII levels include danazol and antiplatelet drugs such as aspirin.[4]

A second heparin cofactor which inhibits thrombin, heparin cofactor II (HCII) was described by Tolefsen et al.[6] Studies indicate that in consumptive coagulopathies such as DIC, a parallel reduction in levels of HCII and ATIII is observed[7]. HCII is thought to contribute to falsely high values in the assays of some genetic ATIII deficiency states[8].

In the present two-stage method[9], thrombin is added to a plasma dilution containing antithrombin III in the presence of LMW heparin. After an initial incubation period (stage 1) residual thrombin is determined with a thrombin-specific chromogenic substrate (stage 2). The residual thrombin activity is inversely proportional to the antithrombin III concentration. A number of studies have shown the validity of this assay approach to the detection of ATIII disorders and deficiencies[5].

The use of bovine thrombin and low heparin levels reportedly reduce the interference of HCII in amidolytic assays[10]. Proprietary formulations used in the manufacture of this ATIII assay have lowered the interference from HCII to a level where discrimination between normal and abnormal levels is similar to that achieved by factor Xa based ATIII assays.

The safety and effectiveness of the Sigma Accucolor Antithrombin III Assay Kit (CRS117A) has been demonstrated by showing its substantial equivalence to Sigma Accucolor Antithrombin III Assay kit (CRS105A) and to Diapharma Coamatic assay. One hundred and fourteen samples with values ranging from 41% normal to 121% normal were assayed using the three kits described above. Using an automated analyzer the current kit (Amelung

AMAX) (y) was compared with the Coamatic assay (MLA-1000C) (x_1). This comparison yielded a correlation coefficient of 0.98 with an equation of $y = 0.91x_1 + 7.85$. When the current kit (y) was compared with Sigma CRS105A (x_2) (both on Amelung AMAX) the comparison yielded a correlation coefficient of 0.93 with an equation of $y = 1.03x_2 - 2.3$. Precision studies demonstrated a within run CV of less than 3% and a total precision of less than 6%. The Sigma Accucolor Antithrombin III Assay Kit (CRS117A) has been determined to be linear to 140%.

1. Rodgers G, Shuman M. Congenital Thrombotic Disorders. 1986 American Journal of Hematology 21:419-430.

2. Rosenberg R, Bauer K. The Heparin-Antithrombin System: A Natural Anticoagulant Mechanism. *In* Hemostasis and Thrombosis; Basic Principles and Clinical Practice, Colman R, Hirsh J, Marder V, and Salzman E. Eds.Third Edition, 1994 pp 837-860. Lippincott Co., Philidelphia, PA. USA.

3. Salem H, Mitchell C, Firkin B. Current Views on the Pathophysiology and Investigations on Thrombotic Disorders. 1987 American Journal of Hematology 25:463-474.

4. Bick R. Clinical Relevance of Antithrombin III. 1982 Seminars in Thrombosis and Hemostasis 8:276-287.

5. Odegard O, Abildgaard U. Antithrombin III: Critical Review of Assay Methods. Signifcance of Variations in Health and Disease. 1978 Hemostasis 7:127-134

6. Tolefsen D, Majerus D, Blank M. Heparin Cofactor II: Purification and Properties of a Heparin-Dependent Inhibitor of Thrombin in Human Plasma. 1982 Journal of Biological Chemistry 257:2162-2169.

7. Tran T, Duckert F. Heparin Cofactor II Determination - Levels in Normals and Patients with Hereditary Antithrombin III Deficiency and Disseminated Intravascular Coagulation. 1984 Thrombosis and Haemostasis 52:112-116.

8. Demers C, Henderson P, Blajchman M, Wells M, Mitchell L, Johnston M, Ofosu F, Fernandez-Rachubinski F, Andrew M, Hirsh J, Ginsberg J. An Antithrombin III Assay Based on Factor Xa Inhibition Provides a More Reliable Test to Identify Congenital Antithrombin III Deficiency Than an Assay Based on Thrombin Inhibition. 1993 Thrombosis and Haemostasis 69:231-235.

9. Odegard O, Lie M, Ablidgaard U. Heparin Cofactor Activity Measured with an Amidolytic Method. 1975 Thrombosis Research 6:287-294.

10. Friberger P, Egberg N, Holmer E, Hellgren M, Blomback M: Antithrombin Assay - The Use of Human or Bovine Thrombin and the Observation of a "Second" Heparin Cofactor. 1982 Thrombosis Research 25:433-436.

510(k) Number (if known): _____

Device Name: Sigma Diagnostics ACCUCOLOR™ Antithrombin III (AT-III)

Indications For Use:

Sigma Diagnostics ACCUCOLOR™ Antithrombin III (AT-III) is used to determine the plasma level of antithrombin III (a substance which acts with the anticoagulant heparin to prevent coagulation). This determination is used to monitor the administration of heparin in the treatment of thrombosis. The determination may also be used in the diagnosis of thrombophilia (a congenital deficiency of antithrombin III).

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

Concurrence of CDRH, Office of Device Evaluation (ODE)

Acting Branch Chief

(Division Sign-Off)
Division of Clinical Laboratory Devices
510(k) Number K972164

Prescription Use ✓ OR Over-The-Counter Use ____
(Per 21 CFR 801.109)