Attachment 4

OCT 22 1998

K982714

Bayer Immuno 1 ™ System

Ferritin Assay

510(k) Method Sheet Summary

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23 July, 1998

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1.0 ..... OVERVIEW

The Bayer Immuno 1 Ferritin Assay originally received 510(k) clearance when the system was first released in 1990. In response to customer inquiries, we are proposing an increase in the concentration of the Level 6 calibrator from 1000 ng/mL to 2500 ng/mL.

This change will prevent unnecessary dilution of high concentration samples required by many customers using this assay while monitoring renal dialysis patients, where the Ferritin levels often exceed 1000 ng/mL.

We propose only two changes to the Method Sheet: Communication of the new calibrator levels and a correlation showing sample recoveries are unchanged between the L6 at 1000 ng/mL and the L6 at 2500 ng/mL. This report summarizes R&D data generated to show that new assay performance is equivalent to previously demonstrated performance.

There is no proposed change to reagents - neither in their manufacture nor formulation.

Table 1. Bayer Immuno 1 Ferritin Assay:
Current and Proposed Calibrators

Calibrator	ng/mL	
	Current	Proposed
L1	0.0	0.0
L2	10.0	10.0
L3	40.0	40.0
L4	100.0	100.0
L5	500.0	1000.0
L6	1000.0	2500.0

2.0 ..... INTRODUCTION

Ferritin is an iron-containing protein predominantly found in the cytoplasm of hepatic and reticulo-endothelial cells. It is the primary storage compound from which iron is mobilized to the transferrin-bound serum pool and thus transferred to red blood cells for use in required body functions. In addition to intracellular ferritin, small but clinically significant amounts are found in circulating serum. The measurement of ferritin in serum is believed to reflect total iron stores of the body.

For this reason, it is important to be able to test ferritin levels from extremely low concentrations to very high concentrations.

Certain disease states are known to elevate serum ferritin concentrations independently of the patient's iron stores. These include hepatic diseases such as cirrhosis, drug or viral-induced necrosis, hepatitis, obstructive jaundice, primary hepatoma and metastatic cancer of the liver. Recently, customers have requested the ability to assay higher concentrations of ferritin without having to dilute patient samples. The Bayer Immuno 1 Ferritin Method in its current formulation allowed for a 2.5 fold increase in sample concentrations to be assayed by adding a new calibrator at 2500 ng/mL.

This change requires no change in formulation of assay reagents. A new Level 6 calibrator at 2500 ng/mL is produced and a previous L5 Calibrator at 500 ng/mL is deleted and replaced with the previous L6 of 1000 ng/mL.

3.0 ..... ASSAY DESCRIPTION

The Bayer Immuno 1 Ferritin (FER) Method uses a homogenous sandwich immunoassay format. Samples are reacted with Ferritin Antibody Conjugate R1 (Antibody linked to FITC) and Ferritin Antibody Conjugate R2 (Antibody linked to calf intestine alkaline phosphatase) and incubated on the Immuno 1 system at 37°C. The anti-Ferritin antibody conjugates combine with sample ferritin to form a sandwich complex, followed by addition of monoclonal Immuno-Magnetic particle (mIMP) Reagent which binds the antibody complexes. After further incubation, the mIMP/antibody complex is washed and a para-nitrophenyl phosphate substrate, which reacts with the enzyme conjugate, is added. The resulting para-nitrophenoxide is monitored at 405 nm and 450 nm using a filter switch protocol. The dose/ response curve is proportional to the amount of ferritin in the sample.

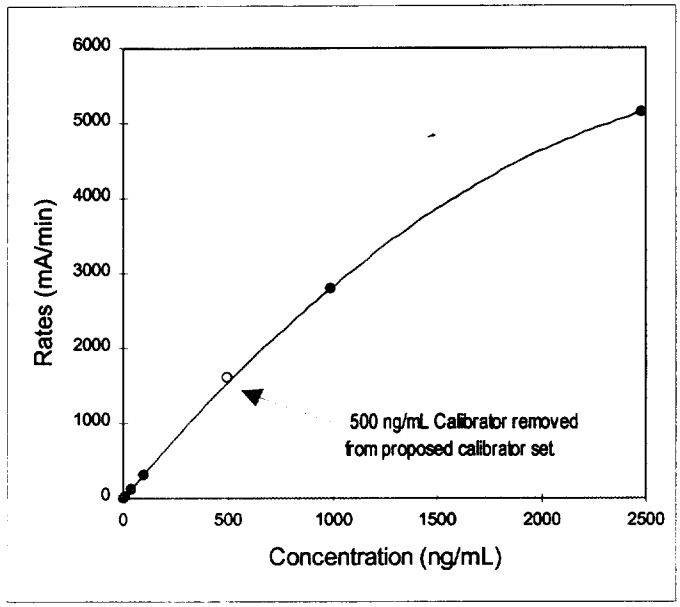

Figure 1. Proposed New Calibration Curve for Bayer Immuno 1 Ferritin Assay. Note: the calibrator at 500 ng/mL was not used to generate this curve and is shown only as a reference to the existing curve.

4.0 ..... CALIBRATORS OVERVIEW

Bayer SETpoint Ferritin Calibrators were first standardized to the World Health Organization (WHO) 1st International Standard (IS 80/602) and the linkage has been perpetuated by nested testing matches of subsequent master lots. Each production lot of calibrators is anchored against a Master Lot and value assigned by comparative analysis of twenty "new" calibrator replicates nested within twenty "master" calibrator replicates. A calibration curve is then generated with the new calibrators and acceptable control and serum pool recoveries are verified before release. Nominal new calibrator values are: 0.0, 10.0, 40.0, 100.0, 1000.0 and 2500.0 ng/mL.

5.0 ..... STABILITY OF NEW 2500 NG/ML CALIBRATOR

Shelf life dating for the new level of Bayer Immuno 1 Ferritin Calibrator will be determined by monitoring recoveries of other calibrators, controls and serum pools under real-time and elevated temperature stressed conditions and compared to -80°C stored components. Data for real-time stability will continue to be generated for at least two years. Additional performance testing will occur at specific time points to verify on-system stability claims for the life-time of the product.

6.0 ..... IMPRECISION

The proposed new Level 6 calibrator does not impact imprecision estimates; no change will be made to the method sheet.

Estimates of imprecision were obtained from replicate analyses of human serum (Pools 1 & 2) and Bayer TESTpoint Ligand Controls (Controls 1 to 3) and then compared to Method Sheet recoveries using the current L6 Calibrator. Method Sheet Imprecision estimates were collected and computed following NCCLS document EP5-T2: Evaluation of Precision Performance of Clinical Chemistry Devices - Second Edition; Tentative Guideline.[2] Precision estimates using the 2500 ng/mL L6 calibrator were generated over 5 days (instead of 20) using four replicates per day, instead of two.

Table 2. Precision Observed for Bayer TESTpoint Controls and Human Serum Pools for Current and Proposed Calibrator Sets: Bayer Immuno 1 Ferritin Assay

	Proposed L6 Calibrator @ 2500 ng/mL					Current method Sheet		
	Pool-1	Control 1	Control 2	Pool-2	Control 3	Control 1	Control 2	Control 3
mean =	**25.2**	**28.8**	**104.6**	**206.7**	**237.4**	**21.1**	**148.1**	**344.2**
Within SD =	0.5	0.5	0.5	8.6	6.0	0.2	3.2	8.5
Within %CV =	1.9	1.8	0.5	4.1	2.5	1.0	2.1	2.5
Total SD =	0.6	0.6	1.4	8.6	6.0	1.5	7.4	17.1
Total %CV =	**2.6**	**2.2**	**1.3**	**4.1**	**2.5**	**7.1**	**5.0**	**5.0**

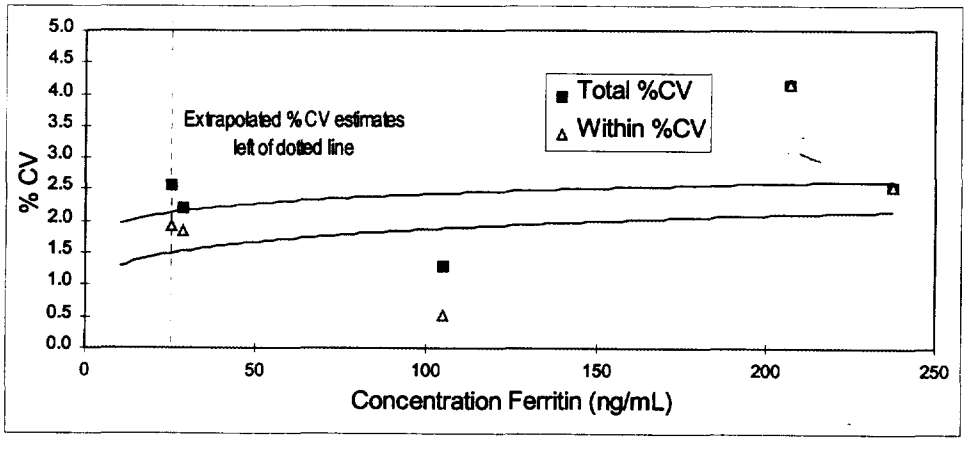

Figure 2 Graph of Within and Total-Run %CV for Bayer Immuno 1 Ferritin Assay.

7.0. ANALYTICAL SENSITIVITY

An estimate of analytical sensitivity (minimal detectable concentration) of the method was determined using Level 1 data generated as part of a performance study comparing multiple systems, reagents and calibrator sets. Analytical Sensitivity is a multi-system estimate of two times the within-run standard deviation of the zero calibrator. This value was determined to be 0.3 ng/mL, unchanged from our current expected value.

8.0. CORRELATION DATA

A total of 102 samples were obtained from outside sources including samples with values greater than the current method's highest calibrator at 1000 ng/mL. Each sample was assayed in singlet using the current Bayer Immuno 1 Ferritin Assay (L6 = 1000 ng/mL) and compared to single results generated using the new extended range Ferritin (L6 = 2500 ng/mL). Three regression analysis plots were generated. The first (n = 72) assesses recoveries of all samples at concentrations less than 1000 ng/mL and will be added to the two comparisons in the current Method Sheet. The second (n = 30) assesses samples greater than 1000 ng/mL, but less than 2500 ng/mL and tests the samples diluted 1:5 in Level 1 calibrator for the current method and neat (undiluted) using the proposed L6 Calibrator method. The third comparison (Figure 5) includes all 102 data points.

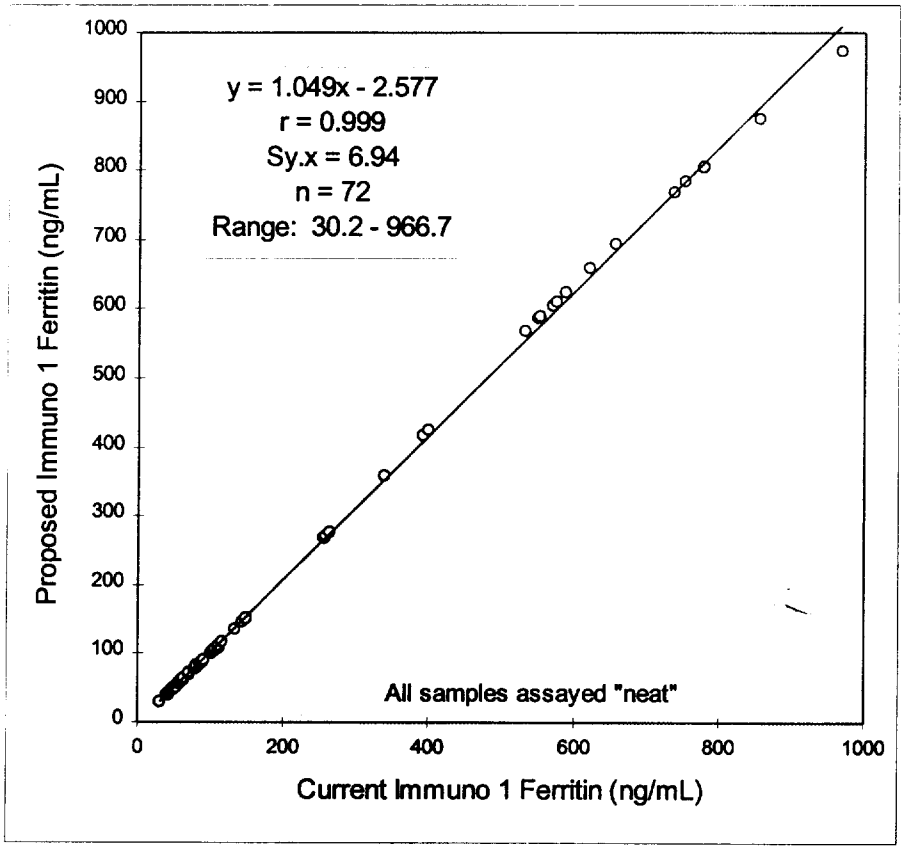

Figure 3. Bayer Immuno 1 Ferritin Assays: Methods Comparison Data (undiluted samples).

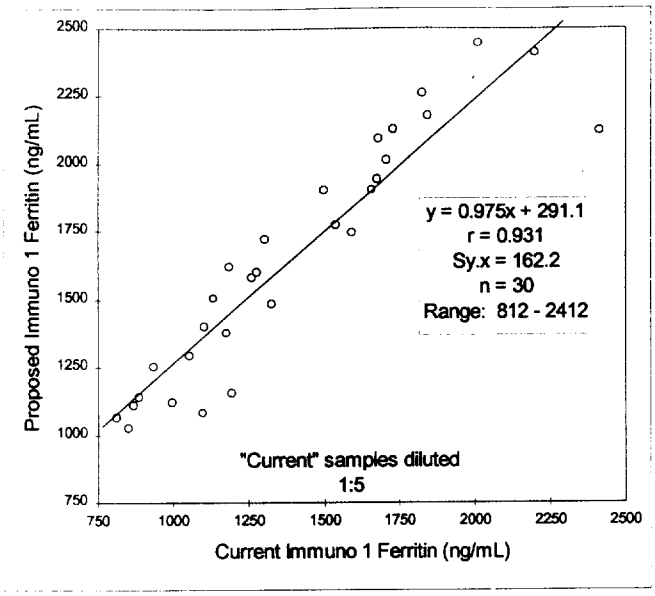

Figure 4. Bayer Immuno 1 Ferritin Assays: Methods Comparison Data (samples >1000 ng/mL diluted for current method).

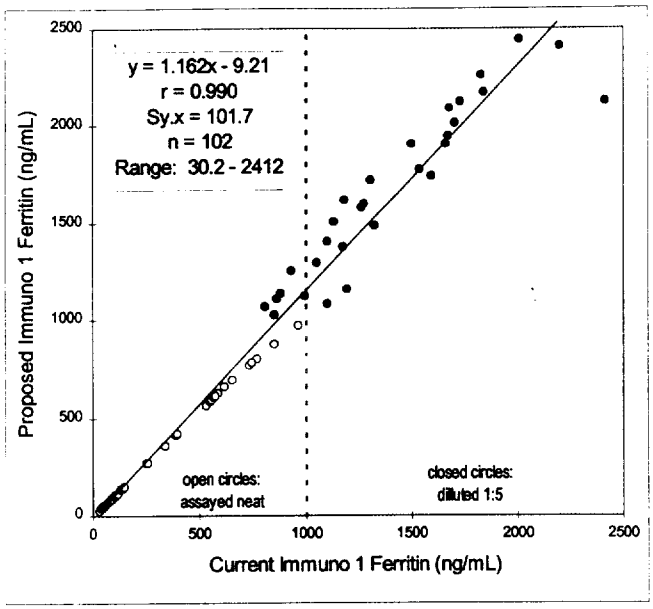

Figure 5. Bayer Immuno 1 Ferritin Assays: Methods Comparison Data (samples >1000 ng/mL diluted for current method).

9.0. ..... SPECIFICITY

Interfering Substances

No reformulations were made to Reagents and the proposed new Level 6 calibrator will not impact specificity. No change will be made to the method sheet.

Cross Reactivity

No reformulations were made to Reagents and the proposed new Level 6 calibrator will not impact cross-reactivity. No change will be made to the method sheet.

10.0..... DILUTION OF OVER-RANGE SAMPLES

No reformulations were made to Reagents and the proposed new Level 6 Calibrator will not impact dilution of high samples. No changes will be made to the method sheet.

This was confirmed by dilution of six samples with concentrations greater than the upper limit of the new analytical range (> 2500 ng/mL). Each sample was diluted 1:10 (1 part sample to 9 parts Bayer Immuno 1 Ferritin Level 1 Calibrator) and tested using both the Current and the Proposed calibration curves.

Results were compared two ways. First a t-test (paired two sample for means) determined no statistical difference between recoveries by the two calibration curves.

Then, a regression analysis between the samples confirmed that the diluted recoveries were equivalent ($r \geq 0.975$, slope ≥ 0.975).

Table 3 T-Test comparing the Results Generated from Six Diluted Patient Samples. The t-Stat is less than the t Critical meaning we cannot say the two populations are different.

t-Test: Paired Two Sample for Means		
	L6 = 1000	*L6 = 2500*
Mean	6074.9	6203.7
Variance	9600749	9454447
Observations	6	6
Pooled Variance	0.998274	
Hypothesized Mean Difference	0	
df	5	
t Stat	-1.725	
t Critical one-tail	2.015	
t Critical two-tail	2.571	
t Stat is < t Critical: Do Not Reject Null Hypothesis		

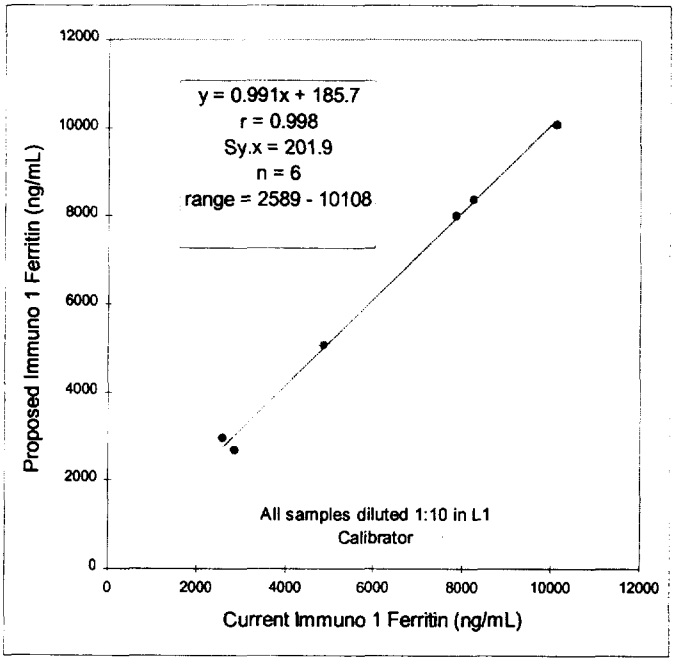

Figure 6. Regression Analysis of Six Diluted Samples using the Current (L6 = 1000 ng/mL) Calibration Curve and the Proposed (L6 = 2500 ng/mL) Calibration Curve.

11.0..... DETERMINATION OF REFERENCE INTERVALS

The change to a higher Level 6 calibrator does not impact sample recoveries, so no new claim is being made.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

OCT 22 1998

Mr. Gabriel J. Muraca, Jr.
Manager Regulatory Affairs
Bayer Corporation
511 Benedict Avenue
Tarrytown, New York 10591

Re: K982714
Trade Name: Bayer Immuno 1™ System Ferritin Assay
Regulatory Class: II
Product Code: DBF
Dated: July 29, 1998
Received: August 4, 1998

Dear Mr. Muraca:

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.

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,

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

510(k) Number (if known): K982714

Device Name: **Bayer Immuno 1™ System**
Ferritin Assay

Indications For Use:

This *in vitro* diagnostic method is intended to quantitatively measure ferritin (an iron-storage protein) in human serum on the Bayer Immuno 1 System. Measurements of ferritin aid in the diagnosis of diseases affecting iron metabolism, such as hemochromatosis (iron overload) and iron deficiency anemia.

This diagnostic method is not intended for use on any other system.

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

Concurrence of CDRH, Office of Device Evaluation (ODE)

(Division Sign-Off)
Division of Clinical Laboratory Devices
510(k) Number K982714

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