OCT - 9 2001

12.0 510(k) Summary

This summary of safety and effectiveness is being submitted in accordance with the requirements of SMDA 1990 and 21 CFR 807.92.

1. **Name of Manufacturer, Contact Person and Date Summary Prepared:**

Nichols Institute Diagnostics
33051 Calle Aviador
San Juan Capistrano, CA 92675
Phone: 949-240-5260
FAX: 949-240-5313
Contact Person: Jimmy Wong, Manager of Clinical and Technical Affairs
Date Prepared: September 20, 2001

2. **Device Name:**

Trade/Proprietary Name:	Nichols Advantage® 25-Hydroxyvitamin D
Common Name:	25-OH-D Immunoassay
Classification Name:	Vitamin D test system

3. **Classification:** Class II

Regulation Number: 862.1825
Product Code: MRG, Clinical Chemistry

4. **Predicate Device:** DiaSorin 25-Hydroxyvitamin D ^{125}I RIA kit

5. **Device Description:**

The Nichols Advantage 25-OH-D (NA 25-OH-D) contains sufficient reagents for 100 tests. The NA 25-OH-D is an automated 25-OH-D assay for use only on the Nichols Advantage Immunoassay System.

6. **Intended Use:**

The Nichols Advantage® 25-Hydroxyvitamin D assay is intended for the quantitative determination of 25-hydrxoyvitamin D (25-OH-D) and other hydroxylated metabolites of vitamin D in serum or plasma to be used as an aid in the assessment of vitamin D sufficiency. Assay results should be used in conjunction with other clinical data to assist the clinician in making individual patient management decisions.

7. **Comparison to Predicate Device:**

The Nichols Advantage 25-OH-D (Y) is substantially equivalent to the DiaSorin 25-Hydroxyvitamin D ^{125}I RIA kit (X). N=99 samples were used in a split sample method comparison study following the NCCLS EP9-A guidelines. For n=80 samples within the reportable ranges of each method, the Passing & Bablok method comparison demonstrates: Y=1.1(X) – 0.6 (95% cf slope: 0.94 to 1.27; 95% cf intercept: -4.6 to 2.1), and a Pearson correlation r=0.84 (95%cf: 0.76-0.89). For the entire n=99 samples, relative agreement using a cut-off of 20 ng/mL or greater was 91%, and the relative agreement for values less than 20 ng/mL was 98%, with an overall agreement of 94%.

8. **Clinical Study**

Patients (n=100) with a diagnosis of chronic renal insufficiency were evaluated with the NA 25-OH-D. Using a cutoff of 20 ng/mL, the results demonstrate the assay recognizes vitamin D deficiency and vitamin D insufficiency, consistent with biochemical measures of disordered calcium mineral ion metabolism. As renal failure becomes progressive worse, the frequency of low 25-OH-D levels increases as do biochemical measures of worsening indices of calcium mineral ion metabolism.

9. Similarities:

- Intended use for each assay is identical.
- Both assays use 25-OH-D_3 in their standards, and both report values using the same units: ng/mL.
- Both assay use the competitive ligand binding technique.
- Both assays are capable of using serum, EDTA and heparinized plasma as samples.

10. Differences:

The following differences pertain to differences in immunoassay technology and do not affect the intended uses of the NA 25-OH-D assay.

Feature	Nichols 25-OH-D	DiaSorin 25-OH-D
Sample Size:	20 uL serum or plasma	50 uL serum or plasma
Solid Phase/Precipitating Complex:	25-OH-D_3 magnetic particles	Donkey anti-goat + normal goat serum + PEG precipitating complex.
Label:	Acridinium-ester labeled Anti-DBP	^{125}I analog o f 25-OH-D_3
Binder/Antibody:	Human vitamin D binding protein	Goat anti-25-OH-D
Technology	Automated, hands free set-up No extraction is required.	Manual procedure Separate extraction is required.
Incubation steps and temperature:	21 minutes @ 37°C (25-OH-D displacement)+ 21 minutes @ 37°C (assay incubation).	90 minutes @ 20-25°C + 20 minutes @ 20-25°C + 20 minutes centrifugation.
Reportable Range	7-120 ng/mL	5.0-100 ng/mL

11. Comparison of Performance Characteristics

Feature	Nichols 25-OH-D	DiaSorin 25-OH-D
Sensitivity	Analytical: 4 ng/mL Functional: 7 ng/mL	Analytical: ≤ 1.5 ng/mL Functional: 2.5 ng/mL (optional std.)
Within-Run Precision (%CV)	3.0-4.5%	8.6-12.5%
Total Precision (%CV)	6.4-14.5%	8.2-11.0%
Recovery	90-99%	92-119%
Linearity	80-109%	96-110%
Specificity @ 50% B/Bo	Vitamin D_2 = 1.6% Vitamin D_3 = 1.2% 25-OH-D_2 = 100% 25-OH-D_3 = 100% 24,25$(OH)_2D_3$ = 100% 25-26-OH_2D_3 = 39% 1,25$(OH)_2D_3$ = 1.1%	Vitamin D_2 = 0.8% Vitamin D_3 = 0.8% 25-OH-D_2 = 100% 25-OH-D_3 = 100% 24,25$(OH)_2D_3$ = 100% 25-26-OH_2D_3 = 100% 1,25$(OH)_2D_3$ = 11.0%

Conclusions: These data, which were provided to FDA, demonstrate safety and effectiveness of the Nichols Advantage 25-Hydroxyvitamin D for the intended in vitro diagnostic use. Furthermore, based on performance characteristics, the Nichols Advantage 25-OH-D assay is substantially equivalent to the predicate method.

10.5 Comparison to a Predicate Device

Method comparison was made against the DiaSorin 25-Hydroxyvitamin D ^{125}RIA kit. Both the predicate device and the subject device were performed exactly as described by their respective manufacturer's directional inserts. The NCCLS Method Comparison (EP9A) procedures were followed. There were n=111 total samples assayed, each in duplicate. The samples were assayed over 3 days in 3 different runs, and quality control samples for each run were within their respective ranges. Of the 111 paired samples, 80 were within the reportable ranges of each method and demonstrated acceptable levels of imprecision. We used 4 standard deviations to delete outliers for reasons of imprecision. Twelve samples demonstrated unacceptable levels of imprecision (>4 sd) and were deleted. Nineteen samples were below the reportable range (<7 ng/mL) with the subject device, and of these, 4 were below the reportable range with the DiaSorin assay (<5 ng/mL). Tabulated data showing the above three groups are located in Appendix 6.

Method comparison statistical analysis was performed with the 80 samples that demonstrated acceptable levels of imprecision. The 80 samples with good precision and the 19 samples that were below the reportable ranges were combined to determine overall concordance using McNemars test. Below is a chart summarizing the levels of imprecision observed in the 80 samples with acceptable levels of imprecision. These data demonstrate that the Nichols Advantage 25-OH-D assay has better within-run precision.

N=80 paired samples	Nichols Advantage 25-OH-D	DiaSorin 25-OH-D
Ave. CV	4.7%	10.6%
Median CV	3.3%	9.1%
Minimum CV	0.1%	0%
Maximum CV	25.4%	35.0%

NCCLS method comparison analysis was performed on the 80 paired samples. The range of results, the Deming method comparison analysis, the Passing and Bablok method comparison, the Pearson correlation, and the NCCLS bias

analysis are summarized in the chart below. These data, and a scatterplot of the entire method comparison are located in Appendix 6.

	Nichols Advantage 25-OH-D (Y)	**DiaSorin 25-OH-D (X)**
Range	7.0-69.5 ng/mL	5.9-88.8 ng/mL
Deming Method Comparison:	**Y**=0.99(**X**) + 0.7 95% confidence slope: 0.85 to 1.14 95% confidence intercept: -3.8 to 5.2	
Passing and Bablok Method Comparison:	**Y**=1.1(**X**) – 0.6 95% confidence slope: 0.94 to 1.27 95% confidence intercept: -4.6 to 2.1	
Pearson correlation	R=0.84 95% confidence: 0.76 to 0.89	
Bias	Ave. bias: 0.6 ng/mL 95% confidence of ave. bias: -1.4 to 2.5 ng/mL 95% confidence of agreement: lower limit: -16.5 ng/mL (-19.7 to –13.2) upper limit: 17.6 ng/mL (14.4 to 20.9)	

Either the Passing and Bablok analysis or the Deming analysis could have been used for describing the method comparison. Because the Passing and Bablok analysis is not dependent upon a constant level of imprecision for the two methods, we think this analysis accurately reflects the comparison between the two methods. The average bias was small, only +0.6 ng/mL, but the upper and lower limits of the bias was large (-16.5 ng/mL to 17.6 ng/mL). The large bias we observed could be due to several reasons. The bias could have been influenced by the larger imprecision we observed with the DiaSorin, and because the crossreactivity of each assay is slightly different for vitamin D sterols. The issue of crossreactivity differences and differences in technology were previously discussed in the Crossreactivity section of this 510k.

Pearson correlation was not ideal because the range of observed results could have been higher. Several high samples were deleted due to poor imprecision obtained using the DiaSorin assay. Here are two examples:

1. Nichols: 101.1, 98.1 vs. DiaSorin: 44.3, 70.8
2. Nichols: 103.8, 100.9 vs. DiaSorin: 89.9, 47.1

We think the Pearson's correlation coefficient would have been higher if those samples were included in the analysis, since the range of results would be

higher. Obtaining samples with high 25-OH-D levels is difficult because levels approaching 100 ng/mL or higher only come from individuals who are ingesting large quantities of vitamin D or are taking pharmacologic doses of vitamin D. Our method comparison study shows good agreement between methods across the reportable ranges, but potentially with large bias for values above approximately 20 ng/mL. The concordance chart below further illustrates this bias.

Concordance chart showing number of sample results falling within the specified ranges. The concordance chart include the 19 samples below the reportable range, and the 80 samples used in the method comparisons.

DiaSorin 25-OH-D (ng/mL)

Adv. 25-OH-D (ng/mL)	0-10	10.1-20	20.1-30	30.1-40	40.1-50	50.1-60	60.1-80	≥80.1
0-10	18	7						
10.1-20	4	16	4	1				
20.1-30			13	1				
30.1-40			11	5	5	1	1	
40.1-50		1	2	3	1			
50.1-60					1	1		1
60.1-80							1	1
≥80.1								0

Using a cutoff of 20 ng/mL or higher, the relative agreement between methods were calculated.
Relative agreement at 20 ng/mL or less: [45/(45+1)] x 100 = 97.8%
Relative agreement at 20 ng/mL and higher: [48/(5+48)] x 100 = 90.6%
Overall agreement using 20 ng/mL as the cutoff: [45+48/99] x 100 = 93.9%

Using a cutoff of 20 ng/mL as the lower limit for vitamin D sufficiency, the subject device demonstrates a relative agreement of 90.6% with the DiaSorin assay at 20 ng/mL and higher. This demonstrates that the subject device is substantially equivalent to the DiaSorin kit in detecting absence of low 25-OH-D levels for determining vitamin D sufficiency. For values below 20 ng/mL, the subject device demonstrates a relative agreement of 97.8% with the DiaSorin kit in identifying low 25-OH-D levels. The overall agreement was 93.9%.

In conclusion, these results in addition to the previous clinical study that evaluates levels of 25-OH-D in patients who are at great risk for vitamin D insufficiency and vitamin D deficiency demonstrate that this device is safe and effective for its intended use.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

OCT - 9 2001

Mr. Jimmy Wong
Manager, Clinical and Technical Affairs
Nichols institute Diagnostics
33051 Calle Aviador
San Juan Capistrano, CA 92675

Re: k012367
Trade/Device Name: Nichols Advantage 25-Hydroxyvitamin D
Regulation Number: 21 CFR 862.1825
Regulation Name: Vitamin D test system
Regulatory Class: Class II
Product Code: JIT, MRG
Regulatory Class: Class I, reserved
Product Code: JJX
Dated: September 26, 2001
Received: September 27, 2001

Dear Mr. Wong:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and 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) that do not require approval of a premarket approval application (PMA). 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 (PMA), 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 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

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" (21CFR 807.97). Other general information on your responsibilities under the Act may be obtained from the Division of Small Manufacturers International and Consumer 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

2.0 Indications For Use Statement

INDICATIONS FOR USE STATEMENT

510(k) Number: K012367

Device Name: Nichols Advantage 25-Hydroxyvitamin D

Indications for Use Statement: The Nichols Advantage® 25-Hydroxyvitamin D assay is for use only on the Nichols Advantage® Specialty System. The Nichols Advantage 25-Hydroxyvitamin D assay is intended for the quantitative determination of 25-hydroxyvitamin D (25-OH-D) and other hydroxylated metabolites of vitamin D in serum or plasma to be used as an aid in the assessment of vitamin D sufficiency in an adult population. Assay results should be used in conjunction with other clinical data to assist the clinician in making individual patient management decisions.

(Please Do Not Write Below This Line – Continue On Another Page If Needed)

Concurrence of CDRH, Office of Device Evaluation (ODE)

✓ **Prescription Use** **Over –The-Counter Use**

(Per 21 CFR 801.109) **Or** **(Optional Format 1-2-96)**

(Division Sign-Off)
Division of Clinical Laboratory Devices
510(k) Number K012367