11.0 510(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
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Contact Person: Jimmy Wong, Manager Clinical and Technical Affairs
Date Prepared: April 19, 2000

2. **Device Name:**
Trade/Proprietary Name: Nichols Institute Diagnostics Chemiluminescence Thyroglobulin
Common Name: Thyroglobulin Immunoassay
Classification Name: Reagent system for the determination of thyroglobulin in human serum.

3. **Classification:** **Class II**
Regulation Number: 866.6010
Product Code: MSW, Immunology

4. **Predicate Device:** **Kronus OptiQuant Thyroglobulin kit**

5. **Device Description:**

The Chemiluminescence Thyroglobulin kit has sufficient reagents for 100 tests. The thyroglobulin assay is a chemiluminescence sandwich immunoassay assay utilizing a biotinylated goat anti-thyroglobulin for capture and a mouse monoclonal antibody labeled with acridinium for detection. A 0.200-mL serum sample is added to a 12x75 mm borosilicate glass tube followed by the addition of 0.100 mL of biotinylated anti-thyroglobulin and 0.050 mL of acridinium labeled anti-thyroglobulin reagents. Samples are also run at a 1/10 dilution (hook detection tube) to check for potentially high samples that may hook in the assay. An avidin-coated bead is then added to the reaction mixture. The assay incubates at room temperature for 16-24 hours on top of a horizontal rotator set at 180 ± 10 rpm. Thyroglobulin in the serum sample binds to the biotinylated antibody and acridinium labeled antibody to form a sandwich-complex. Because of the high affinity between biotin and avidin, the captured sandwich complex binds to the avidin-coated bead. Free biotinylated antibody and acridinium labeled antibody are separated from the complex bound to the bead by aspiration of the reaction mixture and subsequent washing. The tubes containing the washed beads are placed into a luminometer, which automatically injects Trigger 1 and 2, initiating the chemiluminescence reaction. The light is quantified by the luminometer and expressed in relative light units (RLU). The amount of acridinium labeled antibody bound is directly proportional to the concentration of thyroglobulin in the sample. A log-log standard curve is generated by plotting the mean RLU on the ordinate versus the respective concentration of each thyroglobulin standard in ng/mL on the abscissa. The concentration of thyroglobulin is determined directly from the standard curve.

6. **Intended Use:**

The Nichols Institute Diagnostic Chemiluminescence Thyroglobulin is a two-site immunometric assay for the quantitative measurement of thyroglobulin in human serum. The assay is intended to aid in monitoring for the presence of local and metastatic thyroid tissue in patients who have had prior thyroidectomy (using surgery with or without radioiodine). This assay is also indicated for monitoring thyroglobulin levels in combination with radioiodine whole body scans after either rhTSH administration or thyroid hormone withdrawal for detecting presence of thyroid tissue in patients with well-differentiated thyroid cancer. The assay should only be used on patients who lack thyroglobulin autoantibodies.

The presence of autoantibodies against thyroglobulin (TgAb) can interfere with assays for thyroglobulin; hence, the TgAb status of the patient should be determined and reported. Thyroglobulin antibodies can be quantitated with the Nichols Chemiluminescence Thyroglobulin Autoantibodies kit (catalog 60-4185).

The concentration of thyroglobulin (Tg) in a given specimen determined with assays from different manufacturers can vary due to differences in assay methods, reagent specificity, and presence of thyroglobulin autoantibodies. The results reported by the laboratory to the physician must include the identity of the Tg assay used. Values obtained with different assay methods cannot be used interchangeably. If in the course of serially monitoring a patient, the assay method used for determining Tg levels is changed, additional sequential testing should be carried out to confirm baseline values.

7. Comparison to Predicate Device:

The Nichols Institute Diagnostics Chemiluminescence Thyroglobulin is substantially equivalent to another product in commercial distribution with similar intended use. We assert it is substantially equivalent to the Kronus OptiQuant™ Thyroglobulin kit. The following are similarities and differences for each product.

Method Comparison Study: One hundred twenty-one samples were assayed in parallel between the predicate method and the Nichols Tg assay following the NCCLS EP9-A guidelines. Concordance testing on the entire n=121 samples was performed.

Kronus OptiQuant™ Thyroglobulin

Nichols Tg (Y)	<5.0 ng/mL	5.0-9.9 ng/mL	10.0-29.9 ng/mL	30.0-59.9 ng/mL	≥60.0 ng/mL
<5.0 ng/mL	19	1	0	0	0
5.0-9.9 ng/mL	3	8	0	0	0
10.0-29.9 ng/mL	0	4	27	0	0
30.0-59.9 ng/mL	0	0	6	7	1
≥60.0 ng/mL	0	0	0	5	40

Agreement for results less than 60 ng/mL = 93.8%
Agreement for results greater than 60 ng/mL = 97.6%
Relative sensitivity using a cut-off of 5.0 ng/mL or greater = 99%
Relative specificity using a cut-off of less than 5.0 ng/mL = 86%

Similarities:

- Intended use for each kit is similar. That is, both assays are intended to monitor Tg levels in patients after thyroid surgery (with or without radioiodine ablation). Both assays state interference due to thyroglobulin autoantibodies and give warning not to use the assay for patients with thyroglobulin autoantibodies.
- Both assays use specific antibodies to bind and capture thyroglobulin. Both assays use an immunometric approach to measure thyroglobulin in human sera.
- Both assays are standardized to the same CRM457 Thyroglobulin Reference standard and use lyophilized calibrators made from purified human thyroglobulin Both assays report results in the same units - ng/mL.

- The reported expected values in normal healthy adult volunteers are similar for both assays. Using the Kronus Thyroglobulin assay, the reported reference range is 0-60 ng/mL. Using the Nichols Chemiluminescence Thyroglobulin, the reported reference range is 3.2-56.7 ng/mL.
- Both assays incubate overnight at room temperature.

Differences: The differences pertain to differences in immunoassay technology and do not affect the intended uses of each device.

Feature	Nichols Chemiluminescence Thyroglobulin	Kronus Optiquant™ Thyroglobulin Kit
Sample Size	200 uL serum	100 uL serum
Detection Method	Acridinium-ester coupled to monoclonal antibody to Tg; chemiluminescence technology	^{125}I labeled to a monoclonal antibody to Tg
Solid Phase	Avidin-coated bead	Antibody coated tube
Reportable Range	0-100 ng/mL	0-500 ng/mL

Comparison of Performance Characteristics:

Feature	Nichols Chemiluminescence Thyroglobulin	Kronus OptiQuant™ Thyroglobulin Kit
Sensitivity	Analytical = 0.07 ng/mL Functional = 0.5 ng/mL	Analytical = 0.2 ng/mL Functional = 0.35 ng/mL
Intra-Assay Precision (%CV)	N=6; 3.6-6.4 %	N=2; 1.3-2.7 %
Inter-Assay Precision (%CV)	N=10; 3.6-22%	N=2; 5.2-9.9%
Recovery	N=3; 94.2-107.5%	N=4; 96.5-105.2%
Parallelism	N=5; 83-120%	N=4; 88.3-117.3%
High Dose Hook Claim	Up to 1,000 ng/mL	Up to 50,000 ng/mL
Specificity ND = none detected	TSH @5,000 uIU/mL = ND T3 @2,000 ug/dL = ND T4 @40 ug/dL = ND	Not reported
Interference Studies: [Percent recovery]	Hemoglobin @500 mg/dL = 93% Bilirubin @20 mg/dL = 98% Triglyceride @3694 mg/dL = 103%	Hemoglobin = not reported Bilirubin = not reported Triglyceride = not reported

8. Clinical Performance in Patients with Well-Differentiated Thyroid Carcinoma

Nichols Institute Diagnostics obtained permission to use the samples from a published clinical study (Haugen BR et al, 1999 JCEM 84: 3877-3885) that evaluated the use of rhTSH in patients with well-differentiated thyroid cancer. The Tg assay results described in that study were derived from a sensitive Tg radioimmunoassay (Tg RIA). In that study, serum Tg measurements after rhTSH stimulation were evaluated for disease detection when used alone and in combination with radioiodine whole body scan (WBS). The same patient sample cohort used in the Haugen study was also measured using the Nichols Chemiluminescence Thyroglobulin assay (Tg ICMA). Serum Tg was measured while patients were on thyroid hormone therapy at baseline. They then received rhTSH administration (0.9 mg every 24 hours x2 or 0.9 mg every 72 hours x3) with serum Tg testing at 48-hours, and Tg testing plus WBS occurring 72-hours after their final injection of rhTSH. Approximately two weeks after rhTSH administration, patients were then withdrawn from thyroid hormone therapy. While the patients were hypothyroid, serum Tg testing and WBS were again performed. The diagnostic utility of rhTSH administration can then be compared against the traditional combination of withdrawal serum Tg testing and WBS. Up to 162 patients with eligible whole body scan results were analyzed for disease detection using serum Tg ICMA results, with and without WBS, against a diagnostic standard. All n=162 had negative thyroglobulin antibody results.

The ranges of serum Tg ICMA results were determined for four situations during the protocol. First, serum Tg ICMA results at baseline was analyzed against the diagnostic standard, when the patient

was on thyroid hormone therapy (THT). Second, serum Tg ICMA results, 72 hours after final rhTSH administration, were analyzed against the diagnostic standard. [The 72-hour Tg ICMA results were chosen for analysis because it was determined that this time point provided essentially equivalent results to the 48-hour Tg ICMA results.] Third, 72-hour serum Tg ICMA after final rhTSH and rhTSH WBS were combined and analyzed against the diagnostic standard. Fourth, withdrawal serum Tg ICMA results alone was analyzed against the diagnostic standard. We analyzed results using two different diagnostic standards. The first diagnostic standard was used for only THT (baseline) Tg results. This diagnostic standard, by definition, was a positive withdrawal scan and/or a positive post-therapeutic scan or a serum Tg ICMA of 10 ng/mL or more in the absence of a positive scan. The second diagnostic standard, by definition, was the combination of a positive withdrawal WBS and/or a withdrawal serum Tg ICMA of 2.0 ng/mL or more. A positive scan was considered positive for either thyroid remnant and/or disease recurrence. A withdrawal WBS result in which radioiodine uptake was found outside the thyroid bed was considered positive for metastatic disease. Table 1 shows the ranges of serum Tg ICMA levels for each situation on patients considered negative for thyroid tissue. Table 2 shows the ranges of serum Tg ICMA levels for each situation on patients considered positive for thyroid tissue.

Table 1: Percent distribution of serum Tg ICMA levels in patients considered negative for residual or recurrent thyroid tissue. Diagnostic standard was the combination of a withdrawal serum Tg ICMA <2.0 ng/mL and/or a negative withdrawal WBS.

	N	<1.0 ng/mL	1.0-1.9 ng/mL	2.0-4.9 ng/mL	5.0-9.9 ng/mL	10.0-29.9 ng/mL	≥30 ng/mL
THT (baseline)	44	98%	2%	0	0	0	0
Post 72-hr rhTSH administration	45	100%	0	0	0	0	0
Post 72-hr rhTSH plus rhTSH WBS	42	100%	0	0	0	0	0
Combination of withdrawal Tg + WBS	46	74%	26%	0	0	0	0

Table 2: Percent distribution of serum Tg ICMA levels in patients considered positive for residual or recurrent thyroid tissue. When the patient was on THT, the diagnostic standard was a positive withdrawal WBS and/or a serum Tg ICMA of 10 ng/mL or more in the absence of a positive WBS. In the other situations, the diagnostic standard was a positive withdrawal WBS result or a positive post-therapeutic WBS and/or a serum Tg ICMA of 2.0 ng/mL or more.

	N	<1.0 ng/mL	1.0-1.9 ng/mL	2.0-4.9 ng/mL	5.0-9.9 ng/mL	10.0-29.9 ng/mL	≥30 ng/mL
THT (baseline)	48	0	0	17%	10%	19%	54%
Post 72-hr rhTSH administration	83	0	0	14%	11%	27%	48%
Post 72-hr rhTSH plus rhTSH WBS	108	17%	7%	11%	8%	20%	37%
Combination of withdrawal Tg + WBS	117	12%	7%	9%	9%	17%	47%

The diagnostic sensitivity and specificity, positive and negative predictive values, and the diagnostic accuracy of the Nichols Tg ICMA were determined from this study. The following formulas were used (Figure 3).

Figure 3

Sensitivity = $TP \div [TP + FN] \times 100$
Specificity = $TN \div [TN + FP] \times 100$
Positive Predictive Value (PPV) = $TP \div [TP + FP] \times 100$
Negative Predictive Value (NPV) = $TN \div [TN + FN] \times 100$
Accuracy = $[TP + TN] \div total \times 100$
TP = true positive
FP = false positive
TN = true negative
FN = false negative

Traditionally, the hypothyroid WBS in combination with withdrawal Tg testing is superior to either test when used alone. We analyzed the above situations to this standard. Categorically, the receiver operator characteristic for the test is improved using the combination of both withdrawal WBS and serum Tg ICMA testing (Table 3). These results demonstrate the usefulness of combining both the WBS and Tg ICMA testing to improve diagnostic sensitivity and specificity. The diagnostic sensitivity of combined 72-hour rhTSH Tg ICMA testing plus rhTSH WBS to the diagnostic standard was 92%. There were 42 true-negative results, with concordant negative 72-hr rhTSH scans and withdrawal WBS results. Serum Tg ICMA levels were all less than 2.0 ng/mL in these cases. The diagnostic specificity of a negative 72-hour rhTSH scan plus 72-hour Tg ICMA <2.0 ng/mL test to the diagnostic standard was 91% (Table 3). The withdrawal serum Tg ICMA results was also evaluated separately. The diagnostic sensitivity and specificity was 88% and 100%, respectively, when the test was used alone in this cohort.

Table 3: Receiver Operator Characteristics for Nichols Tg ICMA when diagnostic standard was the combined withdrawal WBS and/or a withdrawal serum Tg of 2.0 ng/mL or more.

	Sensitivity	Specificity	PPV	NPV	Accuracy
THT (baseline)	42%	98%	98%	40%	58%
Post 72-hr rhTSH administration	71%	98%	99%	57%	79%
Post 72-hr rhTSH plus rhTSH WBS	92%	91%	96%	82%	92%
Withdrawal Tg testing (alone)	88%	100%	100%	77%	91%

PPV = positive predictive value
NPV = negative predictive value

Conclusions: These data, which were provided to FDA, demonstrate safety and effectiveness of the Nichols Institute Diagnostics Chemiluminescence Thyroglobulin for the intended in vitro diagnostic use.

DEPARTMENT OF HEALTH & HUMAN SERVICES

MAY - 9 2000

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

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

Re: K994140
Trade Name: Nichols Institute Diagnostics Chemiluminescence Thyroglobulin
Regulatory Class: II
Product Code: MSW
Dated: March 10, 2000
Received: March 13, 2000

Dear Mr. Wong:

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" (21CFR 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

4.0 Indications For Use Statement

INDICATIONS FOR USE STATEMENT

510(k) Number: K994140

Device Name: Nichols Institute Diagnostics Chemiluminescence Thyroglobulin

Indications for Use Statement: The Nichols Institute Diagnostics Chemiluminescence Thyroglobulin is a two-site immunometric assay for the quantitative measurement of thyroglobulin in human serum. The assay is intended to aid in monitoring for the presence of local and metastatic thyroid tissue in patients who have had prior thyroidectomy (using surgery with or without radioiodine). This assay is also indicated for monitoring thyroglobulin levels in combination with radioiodine whole body scans after either rhTSH administration or thyroid hormone withdrawal for detecting presence of thyroid tissue in patients with well-differentiated thyroid cancer. The assay should only be used on patients who lack thyroglobulin autoantibodies.

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Concurrence of CDRH, Office of Device Evaluation (ODE)

Peter D. Nelson

(Division Sign-Off)
Division of Clinical Laboratory Devices
510(k) Number K994140

Prescription Use ✓ Or Over-The-Counter Use
(Per 21 CFR 801.109) (Optional Format 1-2-96)