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DEC 20 1999

Request for Evaluation of Automatic
Class III Designation
Section 513(f)(2)

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December 15, 1999

Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Office of Device Evaluation
Food and Drug Administration
9200 Corporate Blvd.
Rockville, MD 20850

Re: K 992284
Trade Name: Wallac's Neonatal Biotinidase Kit, Models NB-1000, NB-4000
Regulatory Class: II
Product Code: NAK
Date of NSE Letter: 11/22/99

Attn: Ms. Carol Benson

Dear Ms. Benson

This document is in response to the letter from ODE dated 11/22/99, replying to our intent to market the above referenced kit, and the determination by ODE that the product is not substantially equivalent (NSE) to devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to any device which has been reclassified into class I (General Controls) or class II (Special Controls). **Based on the Food and Drug Administration Modernization Act of 1997, Section 207, we are requesting that the FDA make a risk-based classification determination of this in-vitro diagnostic device.**

The information provided is consistent with the Guidance Document for Industry and CDRH Staff, entitled " New Section 513 (f) (2)- Evaluation of Automatic Class III Designation..." issued on February 19, 1998 (Section 207 (FDAMA); Section 513(f)(2) of the FDCA; 21USC 360c(f)(2)). This document provides guidance as to the recommendations to be employed by Industry when requesting this determination. The recommendations for information to be submitted should address the following items:

1. A coversheet clearly identifying the submission as "Request for Evaluation of Automatic Class III Designation under 513 (F)(2).
2. The 510(k) number under which the device was found not substantially equivalent.
3. A statement of cross reference to the information contained in the 510(k)

● Page 2

December 15, 1999

4. The classification being recommended under section 513 of the act.
5. A discussion of the potential benefits of the device when compared to the potential or anticipated risk when the device is used as intended.
6. A complete discussion of the proposed general and/or special controls to ensure reasonable assurance of the safety and effectiveness of the device, including whether the product should be exempt from premarket review under section 510(k), whether design controls should be applicable, and what special controls would allow the Agency to conclude the device was reasonably likely to be safe and effective for its intended use.
7. Any clinical or preclinical data not included in the 510(k) that are relevant to the request.

The additional sections of this document address the above items as appropriate. Should there be a need for additional discussion, I can be contacted at 330-825-4525 x 625. Thank you for your time and attention.

Sincerely,



Hank Juske

Director, Regulatory Affairs

Statement of cross reference:

The information contained in the original submission, dated July 2, 1999, and supplemental information submitted on October 6 and 7, 1999, are the basis for the cross-reference in this request. Those cover sheets are attached to provide positive identification of those submitted documents. References in this request should be made to those previously submitted documents.

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Recommended classification under Section 513 of the Act

Based on a review of products similar in nature in the in-vitro diagnostic area, we are requesting that the product be identified as class II, requiring special controls. The request is based on the belief that general controls in and of themselves are not sufficient to provide reasonable assurance of safety and effectiveness. These special controls are identified in the remaining sections of this request.



Potential benefits / risks review of the device

Potential benefits: The assay is intended to provide for the early identification of the inborn error of metabolism characterized by a Biotinidase deficiency (see direction insert from original 510(k) submission). The metabolic error displays a wide variety of symptoms, making diagnosis of the disease difficult by clinical observation alone. Early identification through a neonatal screening program provides a means for early intervention. Treatment with biotin is effective, but early intervention is necessary since neurological damage may not be completely reversed if left untreated. Early intervention through early diagnosis not only provides for improvement in quality of life, but also provides for a more cost-effective method of treatment. Administration of Biotin early can preclude problems associated with long term care of individuals afflicted with neurological disease states.

The methodology provided for in the assay is an improvement in performing the assay currently in use by various labs involved in the neonatal screening process (see "Summary and Explanation of the Assay", direction insert, original 510(k) submission). That methodology is labor intensive since required reagents need to be mixed in the testing lab, and no formal provisions for reagent stability are documented or defined on a consistent basis.

Potential risks: The potential risks associated with the assay are anticipated to be from misdiagnosis or misuse:

1. **Misdiagnosis:** In the event that the kit does not perform as described, the risk is either that a negative newborn is identified as a positive (false positive), or that a positive is not identified as positive (false negative). To try to prevent performance-related problems of either type, control material is provided to assist in the consistent performance of the assay by providing material similar to what is might be expected in the screening lab setting. The requirements for performing the assay are described in detail in the direction insert to provide clarity and consistency in performing the test. Possible interfering substances that may affect results are identified in the direction insert. Performance characteristics regarding linearity, precision and sensitivity are included in the direction insert to provide a clear explanation as to assay function. An extensive section relating to deficient samples is identified in the insert, and a discussion of establishment of the equivocal zone is provided to help understanding of the statistical process.
2. **Misuse:** The misuse of the product could occur by those not trained in the use of the product, or by the procurement of the assay by individuals not authorized to perform the assay. Authorized device distributors convey product to the market, and these distributors require information as to registration of the laboratory or the name of the sponsoring physician. Screening laboratories are typically operated by the individual state governments, and those laboratories are operated under the requirements of CLIA (clinical laboratories improvement act). This should help ensure that those performing the assay meet the requirements identified by CLIA on proficiency and training.



Discussion relating to proposed special controls for the in-vitro diagnostic device

We are proposing that this product should not be exempt from premarket review under section 510(k) of the act. In reviewing similar products submitted to the Food and Drug Administration by PerkinElmer Wallac, we feel it is essentially the same broad type of screening assay as those we have developed in the past. Assays produced by Wallac used in neonatal screening, such as the Phenylalanine assay (K943547) and Leucine assay (K982307) are currently classified as class II devices. In keeping with this scheme, we feel it is appropriate to classify this proposed assay as class II, with the requirement of premarket notification.

During the design phase of this project, design controls as identified in the guidance document "Design Control Guidance for Medical Device Manufacturers" (March 11, 1997, referencing FDA 21CFR 820.30 and Sub-clause 4.4 of ISO 9001), were employed to assist in the development of the product. Design inputs, design outputs, reviews, verification and validation, and transfer issues have been addressed according to internal documents. These processes were addressed at the time of assessment by an external auditor/ registrar, and compliance to the ISO 9001 standard (encompassing requirements for design control) was achieved on September 3, 1999.

The use of external standards was employed during the development of this product. The standards that were employed were typically those suggested by the NCCLS (National Committee for Clinical Laboratory Standards) and the other organizations identified below. The following is a list of referenced standards, referred to in the direction insert for the kit (see original 510(k) submission) or in the development of the product:

1. How to define and determine reference intervals in the clinical laboratory; Approved Guideline. NCCLS Document C28-A, Vol. 15 no.4., June 1995.
2. Method comparison and Bias Estimation using patient samples. NCCLS Approved guideline (IVD) EP9-A. 1995.
3. Blood Collection on Filter Paper for Neonatal Screening Programs; Approved Standard- Third Edition (1997). NCCLS Document LA4-A3. Vol. 17, No 16.
4. Tentative Guideline. User evaluation of precision performance of clinical chemistry devices. EPT-5T2. Volume 12. No. 4. NCCLS
5. Centers for Disease Control (CDC). Infant screening Quality Assurance Program- Semiannual Report-Inborn Errors of Metabolism Vol. 8. No. 1. July 1997
6. Evaluation of Linearity of Quantitative Analytical methods. NCCLS Document EP-6. Vol. 6, No. 18.
7. Interference testing in clinical chemistry proposed guideline. NCCLS Document EP-7, Vol. 6., No. 13.
8. Procedures for the collection of diagnostic blood specimens by skin puncture (1991). Section L-4., NCCLS.
9. Protection of Laboratory Workers from Infectious disease transmitted by blood, body fluids and tissue: Second Edition; Tentative Guideline. NCCLS M29-T2. Vol. 11., No. 14

In addition to employing or referencing the above-recognized external standards, PerkinElmer Wallac participates in the CDC/ APHL Newborn Screening Quality Assurance program. This program specifically relates to Inborn Errors of Metabolism, and provides feedback from various participating laboratories on several metabolic diseases. Biotinidase testing has been added to this panel based for those labs participating in the program for that assay. This participation helps to ensure that the product is consistent with other methodologies in the field, and provides a benchmark for effectiveness of the assay.

Product produced by PerkinElmer Wallac follows the requirements of FDA's QSR to help to ensure the safety and effectiveness of the product.

Clinical data and summary information were submitted previously with the original 510(k) dated July 2, 1999, and subsequent information dated October 6 and October 7, 1999. The information contained in those submissions met the requirements of the agency at that time. If there are additional documents required, these can be conveyed as necessary.

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To: Clinical Chemistry Review Section, Carol Benson

From: Carroll Martin

Re: Premarket Notification Submission for Wallac's Neonatal Biotinidase Assay

July 2, 1999

For several years, Wallac, (formerly Isolab) has been developing a test to measure biotinidase activity in newborn dried blood spots as a screening indicator for biotinidase deficiency. Currently, this disease is screened in state neonatal health labs by PABA (para-amino benzoic acid) assay because a commercial test is not available.

Wallac has conducted studies that we believe demonstrate substantial equivalence to the PABA (para-amino benzoic acid) assay's ability to identify at-risk newborns. In addition, the kit was evaluated at two state labs for comparative purposes against the PABA assay.

In light of the recent FDA Modernization Act, I am asking you to consider this 510(k) submission since there is a medically established method, namely the PABA assay, which has a history of acceptance in the medical community.

If you have further questions, comments or would prefer to schedule a conference to discuss this matter, please feel free to contact me by fax or phone. While the incidence of this disease is very low, the effects on infants with this deficiency are very severe and difficult to diagnose without a prior screening.

Respectfully submitted,

Carroll L. Martin
Regulatory Affairs

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To: Carol Benson, Clinical Chemistry Review Section

From: Hank Juske

Re: Premarket Notification Submission for Wallac's Neonatal Biotinidase Assay
510(k) Number: 992284

October 06, 1999

Dear Ms. Benson,

Per our phone discussion of September 17 with you, Dr. Cooper, Drs. Jackson and Rosenthal, Carroll Martin and myself, I am providing the following supplemental information to that submission. The supplied information is to resolve questions that arose during your review process of this submission. I have paraphrased the questions from you, along with our response to those items.

Please refer to the supplied attachments for the documents or information that was requested. Thanks you for your assistance with this submission.

QUESTIONS/ INQUIRIES AND RESPONSE FROM PHONE CONFERENCE:

1. Q/I: Inappropriate use of the PABA assay as the predicate device.
R: The use of the "de novo" process for this submission was discussed. It was agreed that Wallac would submit the additional requested information to answer the balance of the questions by FDA, and that the FDA would consider the submission in light of the information and make their judgement.
2. Q/I: The FDA requested a statement from Wallac referencing the use of software validation guidelines employed during the development of the software for the equipment.
R: Accompanying is a statement from Wallac regarding the above question. Index item 1.
3. Q/I: There was no inclusion in the submission of Dr. Wolf's paper on the serum assay. There was also no indication of the states where the Biotinidase assayed is mandated.
R: The requested paper regarding Dr. Wolf's publication is included. In addition, states that have mandated that the assay be performed are included. Index item 2.

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To: Carol Benson, Clinical Chemistry Review Section

From: Hank Juske

Re: Premarket Notification Submission for Wallac's Neonatal Biotinidase Assay
510(k) Number: 992284

October 07, 1999

Dear Ms. Benson,

In my re-submission of additional data and information for the above 510 (k), I inadvertently neglected to include an item that was requested in our previous phone conversation. This addition should go into the section in index item 2, and referred to in item three in my cover letter. I apologize for the error on my part.

Sincerely

Hank Juske



Newborn Screening Quality Assurance Program

PERFORMANCE EVALUATION

Quarterly Report Inborn Errors of Metabolism

Volume 12, No. 4

November 1999

The performance evaluation (PE) report is the quarterly summary of all data received within the specified data reporting period for Quarter IV, 1999. The attached tables provide the verification of your reported data, the certification profiles for the distributed specimens, the statistical analyses of quantitative data, and the frequency distributions summary for presumptive clinical (qualitative) assessments. We distribute this PE report to all participants, state laboratory directors, and program colleagues by request.

On October 4, 1999, a panel of five unknown dried-blood spot (DBS) specimens was distributed to all active participants. The DBS panel contained predetermined concentrations of thyroxine (T_4), thyroid-stimulating hormone (TSH), phenylalanine (Phe), total galactose (Gal), 17 α -hydroxyprogesterone (17-OHP), leucine (Leu), and methionine (Met). Special separate panels for biotinidase deficiency and galactose-1-phosphate uridylyltransferase (GALT) deficiency were sent to participating laboratories. We processed data from 141 participants. Data reports submitted in units other than those requested were not accepted and not evaluated. Some data reports were received after the designated due date, and these data were not included in the analyses. All reported data will be analyzed for the annual summary report.

A transcription error (TE) is a mistake in reporting the specimen number. Tran-

scription errors are monitored to provide an indication of attention to detail by laboratory personnel. For the statistical summary analyses, data were not included for values associated with TEs, missing values, values reported as inequalities, values reported as ranges, and values reported in wrong units. Also, data values outside the 99% confidence interval were not included; the number of outliers is listed. Results of our evaluation of the panel specimens indicate that the endogenous levels of T_4 , TSH, Gal, and 17-OHP were negligible, and the endogenous levels of Phe, Leu, and Met were less than 2.0 mg/dL whole blood.

Presumptive clinical classifications (qualitative assessments) may differ by participant because of specific clinical assessment practices. For participants that have provided us with their cutoff values, we applied those cutoffs in our final appraisal of the error judgment. *Clinical assessment not evaluated (NE)* is shown for specimens containing analyte concentrations that are subject to different interpretations (i.e., specimens with enrichments near the cutoff value or preliminary survey specimens that are under research evaluation for adequacy of performance). GALT specimens are not evaluated for clinical assessment errors. Because manufacturers do not routinely analyze patient specimens, their clinical assessments are omitted.

Overall (not including the preliminary survey for GALT), participants reported 8 false-positive clinical assessments and 5

false-negative clinical assessments. Participant-specific cutoff values were applied when a nonmatch occurred between the expected and the reported clinical assessments. Eleven reported clinical assessments, which were otherwise incorrect, were judged correct by this procedure. There were 80 transcription errors in the reported data. After the reporting deadline, we do not accept changes to the quantitative results or the clinical assessment codes because such changes would mask a laboratory's true performance and skew the overall performance of program participants. ❖

The Newborn Screening Quality Assurance Program will ship next quarter's PE specimens on January 10, 2000; the next major allotment of quality control specimens is scheduled for shipping on January 10, 2000. ❖

SpotLight

During a public conference in May 1999, the American Academy of Pediatrics' Task Force on Newborn Screening, consisting of physicians, parents, ethicists, directors of state public health laboratories, policy-makers and other individuals involved in screening and intervention, heard comments to five workgroup reports. The comments received at the conference, and subsequent reviews, have been incorporated into the final report, *Blueprint for the Future: Recommendations from the Newborn Screening Task Force*. The report will be submitted to *Pediatrics* with request for publication as a Supplement. ❖

This program is cosponsored by the Centers for Disease Control and Prevention (CDC) and the Association of Public Health Laboratories (APHL).

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CDC
CENTERS FOR DISEASE CONTROL
AND PREVENTION

000011

NEWBORN SCREENING QUALITY ASSURANCE PROGRAM

QUARTER IV - NOVEMBER 1999

DATA VERIFICATION

LAB 325

Analyte	Specimen 9941		Specimen 9942		Specimen 9943		Specimen 9944		Specimen 9945	
	Result	Code								
Thyroxine										
TSH										
Phe	0.3		0.0		0.3		5.6		5.6	
Galactose	24.5		22.9		22.2		18.2		4.5	
17 - OHP										
Leucine	2.8		1.6		1.7		9.0		3.0	
Methionine										

Analyte	Specimen 9491		Specimen 9492		Specimen 9493		Specimen 9494		Specimen 9495	
GALT	1.3		3.2		7.1		4.2		8.1	

Codes: 01, 11, 21 = within normal limits 02, 12, 22 = outside normal limits

Analyte	Specimen 9471		Specimen 9472		Specimen 9473		Specimen 9474		Specimen 9475	
Biotinidase	29.6		31.9		115.8		231.8		236.1	

Codes: 01 = normal activity 02 = deficiency 03 = partial deficiency

* = no quantitative data reported

T.E. = transcription error

REVIEWER'S COMMENTS

If you have any questions about your results, please contact the Newborn Screening Quality Assurance Program Office at: (770) 488-4582 or FAX: (770) 488-4255.

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NEWBORN SCREENING QUALITY ASSURANCE PROGRAM

QUARTER IV - NOVEMBER 1999

SPECIMEN CERTIFICATION

ENRICHMENT LEVELS*

Analyte	Specimen 9941xx	Specimen 9942xx	Specimen 9943xx	Specimen 9944xx	Specimen 9945xx
Thyroxine ($\mu\text{g/dL}$ serum)**	7.5	5.7	10.7	14.4	15.3
TSH ($\mu\text{U/mL}$ serum)	30	70	15	14	8
Phenylalanine (mg/dL whole blood)	0	0	0	6.5	6.5
Galactose (mg/dL whole blood)	22	24	25	20	0
17-OHP (ng/mL serum)	70	10	60	25	75
Leucine (mg/dL whole blood)	0	0	0	6.5	0
Methionine (mg/dL whole blood)	4	0	0	0	1

*endogenous levels not included

**CDC assayed values

EXPECTED CLINICAL ASSESSMENTS

	Specimen 9941xx	Specimen 9942xx	Specimen 9943xx	Specimen 9944xx	Specimen 9945xx
Hypothyroidism	NE	02, 12, 22	NE	NE	01, 11, 21
Phenylketonuria	01	01	01	02	02
Galactosemia	02	02	02	02	01
Congenital Adrenal Hyperplasia	02	01	02	NE	02
Maple Syrup Urine Disease	01	01	01	02	01
Homocystinuria	02	01	01	01	NE
	Specimen 9491xx	Specimen 9492xx	Specimen 9493xx	Specimen 9494xx	Specimen 9495xx
Galactose-1-Phosphate Uridyltransferase Disorder	02	01	01	01	01

01, 11, 21 = within normal limits

02, 12, 22 = outside normal limits

NE = clinical assessment not evaluated

EXPECTED CLINICAL ASSESSMENTS

	Specimen 9471xx	Specimen 9472xx	Specimen 9473xx	Specimen 9474xx	Specimen 9475xx
Biotinidase Deficiency	02	02	01	01	01

01 = normal activity

02 = deficiency

03 = partial deficiency

NE = clinical assessment not evaluated

000013

000014

FOOD AND DRUG ADMINISTRATION
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FACSIMILE TRANSMITTAL SHEET

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Here is the petition. If you need anything else, please let me know.
