



Food and Drug Administration  
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December 15, 2014

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Re: DEN140010  
EnLite™ Neonatal TREC Kit  
Evaluation of Automatic Class III Designation – *De Novo* Request  
Regulation Number: 21 CFR 866.5930  
Regulation Name: Newborn Screening Test for SCID  
Regulatory Classification: Class II  
Product Code: PJI  
Dated: October 12, 2014  
Received: October 14, 2014

Dear Ms. Taylor:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your *de novo* request for classification of the EnLite™ Neonatal TREC Kit, a prescription device. The intended use of the EnLite™ Neonatal TREC Kit is:

The EnLite™ Neonatal TREC Kit is an in vitro diagnostic device intended for the semi-quantitative determination of TREC (T-cell receptor excision circle) DNA in blood specimens dried on filter paper. The test is for use on the VICTOR™ EnLite instrument. The test is indicated for use as an aid in screening newborns for severe combined immunodeficiency disorder (SCID). The test is not intended for use as a diagnostic test or for screening of SCID-like syndromes, such as DiGeorge Syndrome, or Omenn Syndrome. It is also not intended to screen for less acute SCID syndromes such as leaky-SCID or variant SCID.

FDA concludes that this device, and substantially equivalent devices of this generic type, should be classified into class II. This order, therefore, classifies the EnLite™ Neonatal TREC Kit, and substantially equivalent devices of this generic type, into class II under the generic name, Newborn Screening Test for SCID.

FDA identifies this generic type of device as: Newborn Screening Test for SCID

A newborn screening test for severe combined immunodeficiency syndrome (SCID) is a prescription device intended to measure T-cell receptor excision circle (TREC) DNA obtained from dried blood spot specimens on filter paper using a polymerase chain reaction (PCR) based test as an aid in screening newborns for SCID. Presumptive positive results must be followed-up by diagnostic

confirmatory testing. This test is not intended for use as a diagnostic test, or for screening of SCID-like syndromes, such as DiGeorge syndrome or Omenn syndrome. It is also not intended to screen for less acute SCID syndromes, such as leaky SCID or variant SCID.

Section 513(f)(2) of the Food, Drug and Cosmetic Act (the FD&C Act) was amended by section 607 of the Food and Drug Administration Safety and Innovation Act (FDASIA) on July 9, 2012. This new law provides two options for *de novo* classification. First, any person who receives a "not substantially equivalent" (NSE) determination in response to a 510(k) for a device that has not been previously classified under the Act may, within 30 days of receiving notice of the NSE determination, request FDA to make a risk-based classification of the device under section 513(a)(1) of the Act.

Alternatively, any person who determines that there is no legally marketed device upon which to base a determination of substantial equivalence may request FDA to make a risk-based classification of the device under section 513(a)(1) of the Act without first submitting a 510(k). FDA shall, within 120 days of receiving such a request, classify the device. This classification shall be the initial classification of the device. Within 30 days after the issuance of an order classifying the device, FDA must publish a notice in the **Federal Register** classifying the device type.

On February 18, 2014, FDA received your *de novo* requesting classification of the EnLite™ Neonatal TREC Kit into class II. The request was submitted under section 513(f)(2) of the FD&C Act. In order to classify the EnLite™ Neonatal TREC Kit into class I or II, it is necessary that the proposed class have sufficient regulatory controls to provide reasonable assurance of the safety and effectiveness of the device for its intended use.

After review of the information submitted in the *de novo* request FDA has determined that the EnLite™ Neonatal TREC Kit intended for use as follows:

The EnLite™ Neonatal TREC Kit is an in vitro diagnostic device intended for the semi-quantitative determination of TREC (T-cell receptor excision circle) DNA in blood specimens dried on filter paper. The test is for use on the VICTOR™ EnLite™ instrument. The test is indicated for use as an aid in screening newborns for severe combined immunodeficiency disorder (SCID). The test is not intended for use as a diagnostic test or for screening of SCID-like syndromes, such as DiGeorge syndrome, or Omenn syndrome. It is also not intended to screen for less acute SCID syndromes such as leaky-SCID or variant SCID.

can be classified in class II with the establishment of special controls for this type of device. FDA believes that the class II special controls identified later in this order, along with the applicable general controls, provide reasonable assurance of the safety and effectiveness of the device type.

**Table 1 – Identified Risks to Health and Required Mitigations**

<b>Identified Potential Risks</b>	<b>Required Mitigations</b>
False negative results due to device or user error	Special controls (1) and (2)
False positive results due to device or user error	Special controls (1) and (2)

In addition to the general controls of the FD&C Act, the Newborn Screening Test for SCID is subject to the following special controls:

- 1) Premarket notification submissions must include the following information:
  - i. The intended use must indicate:
    - A) The test is not intended for diagnostic use, or for screening of SCID-like syndromes, such as DiGeorge syndrome or Omenn syndrome, and
    - B) The test is not intended to screen for less acute SCID syndromes, such as leaky SCID or variant SCID.
  - ii. A detailed description of all components in the test that includes:
    - A) A detailed description of the test components, all required reagents, instrumentation and equipment, including illustrations or photographs of non-standard equipment or methods.
    - B) Detailed documentation of the device software including, but not limited to, standalone software applications and hardware-based devices that incorporate software.
    - C) Specifications for the filter paper, which must be appropriately labeled for in vitro diagnostic use, to be used in specimen collection and how it will be used in specimen collection validation. These specifications must include: descriptive characteristics of the filter paper, instructions on how a lab should choose the appropriate filter paper, chemical properties of the filter paper, interference concerns associated with the chemicals in the filter paper, and absorption properties of the filter paper, punch size, absorption capacity, testing for homogeneity of punches, diameter of the circle for the dried blood spot aliquot, absorption time, physical composition, and number and size of punches to be tested.
    - D) Methodology and protocols for detection of T-cell receptor excision circles and methods for determination of results. The cut-off must be selected before conducting clinical and analytical studies.
    - E) A description of the result outputs along with sample reports. Sample reports must include the scale used in reporting of results (e.g., TREC copies/ $\mu$ L) and the range of values that will be reported out.
    - F) A description of appropriate internal and external controls that are recommended

or provided. The description must identify those control elements that are incorporated into the testing procedure.

iii. Information that demonstrates the performance characteristics of the test, including:

- A) Data that demonstrates the clinical validity of the device, using well characterized prospectively or retrospectively obtained clinical specimens representative of the intended use population. A minimum of 10-15 confirmed positive specimens must be obtained from more than one site, including relevant annotation, and, at one year or beyond, a SCID diagnosis by flow cytometry or clinically meaningful information regarding the status of the subject must be obtained. Additional specimens should have been obtained that are characterized by other disorders that can be found by screening specimens that have low or absent TREC (e.g., other T-cell lymphopenic disorders) to supplement the range of results. The clinical validation study must have a pre-specified clinical decision point (i.e., cut-off to distinguish positive and negative results). Results must be summarized in tabular format comparing interpretation of results to the reference method. Point estimates together with two-sided 95 percent confidence intervals must be provided for the positive percent agreement (PPA), negative percent agreement (NPA) and overall percent agreement (OPA). Data must include the retest rate, the false positive rate before retest, the final false positive rate, and the false negative rate.
- B) Device reproducibility data generated, using a minimum of three sites of which at least two must be external sites, with two operators at each site. Each site must conduct a minimum of 5 runs per operator over 5 non-consecutive days evaluating a minimum of six different relevant TREC concentrations that span and are well distributed over the measuring range and include the clinical cut-off. Specimens must include cord blood and cord blood diluted with ABO matched adult blood specimens. Identical specimens from the same sample panel must be tested at each site. Each specimen must be run in triplicate and include controls run in triplicate. Results must be reported as the standard deviation and percentage coefficient of variation for each level tested. Results must also be displayed as a dichotomous variable around the cut-off. Total variation must be partitioned into the sum of within-lab and between-lab variations with pre-specified acceptance criteria and 95 percent confidence intervals for all data. Pre-specified acceptance criteria must be provided and followed.
- C) Device precision data using clinical samples to evaluate the within-lot, between-lot, within-run, between run and total variation. A range of TREC levels of the specimen must include samples within the measuring range, samples above and

below the measuring range, as well as with samples very near above and below the cut-off value. At least three replicates of each specimen must be tested with controls and calibrator(s) according to the device instructions for use. The precision study must use well characterized samples using different lots, instruments and operators. Results must be summarized in tabular format. Pre-specified acceptance criteria must be provided and followed.

- D) Linearity of the test must be demonstrated using a dilution panel from clinical samples. The range of dilution samples must include samples within the measuring range, samples above and below the measuring range, as well as with samples very near above and below the cut-off value. Results of the regression analysis must be summarized in tabular format and fitted into a linear regression model with the individual measurement results against the dilution factors. Pre-specified acceptance criteria must be provided and followed.
- E) Device analytic sensitivity data, including limit of blank, limit of detection, and limit of quantification.
- F) Device specificity data, including interference, carryover, cross-contamination, and in silico analysis of potential off-target genomic sequences.
- G) Device stability data, including real-time stability of samples under various storage times, temperatures, and freeze-thaw conditions. A separate shipping stability study must be performed.
- H) Lot-to-lot reproducibility study of each filter paper that will be validated with the test. The lot-to-lot study must include a minimum of three lots of each blood spot card that will be validated with the test and be conducted over 5 non-consecutive days. The sample panel must consist of specimens with a range of TREC levels and include samples within the measuring range, samples above and below the measuring range, and samples very near above and below the cut-off value. Multiple punches must be obtained from each card for demonstration of homogeneity of the analyte across the dried blood spot. Comparability of the test performance for each filter paper must be demonstrated. Stability and storage of TREC DNA on each blood spot card must be demonstrated. Results of the lot-to-lot study must be summarized providing the mean, standard deviation, and percentage coefficient of variation in a tabular format. Data must be calculated for the within-run, between-run, within-lot, and between-lot. Data demonstrating the concordance between results across different filter papers must be provided. . Study acceptance criteria must be provided and followed.

- I) If applicable, a thermocycler reproducibility study must be performed using thermocyclers from three independent thermocycler manufacturers. The sample panel must consist of specimens with a range of TREC levels and must include samples within the measuring range, samples above and below the measuring range, and samples very near above and below the cut-off value. The study must be done using 3 filter paper lots and conducted over 5 non-consecutive days. Results of the thermocycler reproducibility study must be summarized providing the mean, standard deviation, and percentage coefficient of variance in a tabular format. Data must be calculated for the within-run, between-run, within-lot, between-lot and between thermocycler manufacturer study results. Study acceptance criteria must be provided and followed.
  - iv. Identification of risk mitigation elements used by your device, including a description of all additional procedures, methods and practices incorporated into the directions for use that mitigate risks associated with testing.
- 2) Your 809.10 compliant labeling must include:
- i. A warning statement that reads, “This test is not intended for diagnostic use, pre-implantation or prenatal testing, or for screening of SCID-like syndromes, such as DiGeorge syndrome or Omenn syndrome. It is also not intended to screen for less acute SCID syndromes, such as leaky SCID or variant SCID.”
  - ii. A warning statement that reads, “Test results are intended to be used in conjunction with other clinical and diagnostic findings, consistent with professional standards of practice, including confirmation by alternative methods and clinical evaluation, as appropriate.”
  - iii. A description of the performance studies listed in section 1(iii) and a summary of the results.
  - iv. A description of the filter paper specifications required for the test.

In addition, this is a prescription device. Section 510(m) of the FD&C Act provides that FDA may exempt a class II device from the premarket notification requirements under section 510(k) of the FD&C Act, if FDA determines that premarket notification is not necessary to provide reasonable assurance of the safety and effectiveness of the device type. FDA has determined premarket notification is necessary to provide reasonable assurance of the safety and effectiveness of the device type and, therefore, the device is not exempt from the premarket notification requirements of the FD&C Act. Thus, persons who intend to market this device type must submit a premarket notification containing information on the Newborn Assay for SCID they intend to market prior to marketing the device and receive clearance to market from FDA.

Please be advised that FDA’s decision to grant this *de novo* request does not mean that FDA has made a determination that your device complies with other requirements of the FD&C Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the

FD&C Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); 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 FD&C Act); 21 CFR 1000-1050.

A notice announcing this classification order will be published in the **Federal Register**. A copy of this order and supporting documentation are on file in the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852 and are available for inspection between 9 a.m. and 4 p.m., Monday through Friday.

As a result of this order, you may immediately market your device as described in the *de novo* request, subject to the general control provisions of the FD&C Act and the special controls identified in this order.

If you have any questions concerning this classification order, please contact Caryl Giuliano at 301-796-2478.

Sincerely yours,

**Reena Philip -S**

Reena Philip, Ph.D.

Director

Division of Molecular Genetics and Pathology

Office of *In Vitro* Diagnostics and Radiological Health

Center for Devices and Radiological Health

**Concurrence & Template History Page**  
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Full Submission Number: DEN140010

<b>Digital Signature Concurrence Table</b>	
Reviewer Sign-Off	Caryl Giuliano
Branch Chief Sign-Off	Donna Roscoe
Division Sign-Off	Reena Philip -S 2014.12.15 15:50:10 -05'00'
Office Sign-Off	

Template Name: 1a – Order Granting the De Novo

Template History:

Date of Update	Updated By	Description of Update
10/26/2012	MMJ	Updated language to align with FDASIA. Placed in Digital Signature format.
11/27/2012	MMJ	Updated sig block to show Joni Foy’s new title.
12/4/2012	MMJ	Updated Digital Signature table to add a block for Office-level signoff.
12/12/2012	MMJ	One digit was missing from 4-digit ZIP code extension in letterhead (“002” should read “0002”). Revised to fix this.
1/29/2014	MMJ	Revised to reflect OCC’s recent feedback to OIR on recommended content for letters granting de novos, and to add some more minor edits provided by Joni Foy.
1/31/2014	MMJ	Added paragraph regarding compliance w/other requirements of the Act.
3/4/2014	MMJ	1 <sup>st</sup> full paragraph on page 2, titled “[If Class II, choose this paragraph 2]:” Changed 1 <sup>st</sup> sentence from “In addition to…” to “In combination with…”
3/17/2014	MMJ	Changed instructions on page 1 to “Exact name of CFR regulation - associated identification; do not list the regulation number”
4/11/2014	MMJ	Added correct acronyms for the FD&C Act
6/4/2014	MMJ	Updated address block to align w/510k and 513g boilers
9/11/2014	MMJ	Updated header to say ‘de novo number’