



Food and Drug Administration
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June 29, 2017

Re: DEN160047
ClearLLab Reagents (T1, T2, B1, B2, M)
Evaluation of Automatic Class III Designation – *De Novo* Request
Regulation Number: 21 CFR 864.7010
Regulation Name: Flow Cytometric Test System for Hematopoietic Neoplasms
Regulatory Classification: Class II
Product Code: PWD
Dated: October 3, 2016
Received: October 3, 2016

Dear Mr. Dennis:

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 ClearLLab Reagents (T1, T2, B1, B2, M), a prescription device. The ClearLLab Reagents is indicated for use as follows:

The ClearLLab reagents are intended for in vitro diagnostic use as a panel for qualitative identification of cell populations by multiparameter immunophenotyping on an FC 500 flow cytometer. These reagents are used as an aid in the differential diagnosis of hematologically abnormal patients having, or suspected of having the following hematopoietic neoplasms: chronic leukemia, acute leukemia, non-Hodgkin lymphoma, myeloma, myelodysplastic syndrome (MDS), and/or myeloproliferative neoplasms (MPN). The reagents can be used with peripheral whole blood collected in EDTA (K2 and K3EDTA), Acid Citrate Dextrose or Heparin, bone marrow collected in K2EDTA, ACD, or Heparin, and lymph node specimens. Interpretation of the results should be confirmed by a pathologist or equivalent professional in conjunction with other clinical and laboratory findings.

These reagents provide multiparameter, qualitative results for the Cluster of Differentiation (CD) parameters listed below:

- ClearLLab T1: CD2, CD56, CD7, CD5, CD45
- ClearLLab T2: CD8, CD4, CD3, CD45
- ClearLLab B1: Kappa, Lambda, CD19, CD5, CD45
- ClearLLab B2: CD20, CD10, CD19, CD38, CD45

- ClearLLab M: CD7, CD13, CD34, CD33, CD45

FDA concludes that this device, and substantially equivalent devices of this generic type, should be classified into class II. This order, therefore, classifies the ClearLLab Reagents (T1, T2, B1, B2, M), and substantially equivalent devices of this generic type, into class II under the generic name, “Flow Cytometric Test System for Hematopoietic Neoplasms.”

FDA identifies this generic type of device as: **Flow Cytometric Test System for Hematopoietic Neoplasms.**

A flow cytometric test for hematopoietic neoplasms is a device that consists of reagents for immunophenotyping of human cells in relation to the level of expression, antigen density, and distribution of specific cellular markers. These reagents are used as an aid in the differential diagnosis or monitoring of hematologically abnormal patients having or suspected of having hematopoietic neoplasms. The results should be interpreted by a pathologist or equivalent professional in conjunction with other clinical and laboratory findings.

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 October 3, 2016, FDA received your *de novo* requesting classification of the ClearLLab Reagents (T1, T2, B1, B2, M) into class II. The request was submitted under section 513(f)(2) of the FD&C Act. In order to classify the ClearLLab Reagents (T1, T2, B1, B2, M) 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 ClearLLab Reagents (T1, T2, B1, B2, M) indicated for use as follows:

The ClearLLab reagents are intended for in vitro diagnostic use as a panel for qualitative identification of cell populations by multiparameter immunophenotyping on an FC 500 flow cytometer. These reagents are used as an aid in the differential diagnosis of hematologically abnormal patients having, or suspected of having the following hematopoietic neoplasms: chronic leukemia, acute leukemia, non-Hodgkin lymphoma, myeloma, myelodysplastic syndrome (MDS), and/or myeloproliferative neoplasms

(MPN). The reagents can be used with peripheral whole blood collected in EDTA (K2 and K3EDTA), Acid Citrate Dextrose or Heparin, bone marrow collected in K2EDTA, ACD, or Heparin, and lymph node specimens. Interpretation of the results should be confirmed by a pathologist or equivalent professional in conjunction with other clinical and laboratory findings.

These reagents provide multiparameter, qualitative results for the Cluster of Differentiation (CD) parameters listed below:

- ClearLLab T1: CD2, CD56, CD7, CD5, CD45
- ClearLLab T2: CD8, CD4, CD3, CD45
- ClearLLab B1: Kappa, Lambda, CD19, CD5, CD45
- ClearLLab B2: CD20, CD10, CD19, CD38, CD45
- ClearLLab M: CD7, CD13, CD34, CD33, CD45

can be classified in class II with the establishment of special controls for class II. FDA believes that class II (special) controls provide reasonable assurance of the safety and effectiveness of the device type. The identified risks and identified mitigations associated with the device type are summarized in Table 1.

Table 1 - Identified Risks to Health and Identified Mitigations

Identified Risks to Health	Identified Mitigations
Incorrect test results (false negatives or false positives)	General Controls and Special Controls (1) and (2)
Incorrect interpretation of device results by the end user	General Controls and Special Controls (1), (2), and (3)
Patient harm from specimen(s) collection	General Controls and Special Control(1)

In combination with the general controls of the FD&C Act, a Flow Cytometric Test System for Hematopoietic Neoplasms is subject to the following special controls:

1. Premarket notification submissions must include the following information:
 - i. The indications for use must indicate the clinical hematopoietic neoplasms for which the assay was designed and validated, for example, chronic leukemia or lymphoma.
 - ii. A detailed device description including the following:
 - (A) A detailed description of all test components, all required reagents, and all instrumentation and equipment, including illustrations or photographs of nonstandard 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) A detailed description of methodology and assay procedure.
 - (D) A description of appropriate internal and external quality control materials that are recommended or provided. The description must identify those control elements that are incorporated into the testing procedure, if applicable.
 - (E) Detailed specifications for sample collection, processing, and storage.
 - (F) Detailed specification of the criteria for test results interpretation and reporting including pre-established templates.
 - (G) If applicable, based on the output of the results, a description of the specific number of events to collect, result outputs, and analytical sensitivity of the assay that will be reported.
- iii. Information that demonstrates the performance characteristics of the test, including:
- (A) Device performance data from either a method comparison study comparing the specific lymphocyte cell markers to a predicate device or data collected through a clinical study demonstrating clinical validity using well-characterized clinical specimens. Samples must be representative of the intended use population of the device including hematologic neoplasms and the specific sample types for which the test is indicated for use.
 - (B) If applicable, device performance data from a clinical study demonstrating clinical validity for parameters not established in a predicate device of this generic type using well-characterized prospectively obtained clinical specimens including all hematologic neoplasms and the specific sample types for which the device is indicated for use.
 - (C) Device precision data using clinical samples to evaluate the within-lot, between-lot, within-run, between run, site-to-site and total variation using a minimum of three sites, of which at least two sites must be external sites. Results shall be reported as the standard deviation and percentage coefficient of variation for each level tested.
 - (D) Reproducibility data generated using a minimum of three lots of reagents to evaluate mean fluorescence intensity and variability of the recovery of the different markers and/or cell populations.
 - (E) Data from specimen and reagent carryover testing performed using well-established methods (e.g., CLSI H26-A2).
 - (F) Specimen and prepared sample stability data established for each specimen matrix in the anticoagulant combinations and storage/use conditions that will be indicated.
 - (G) A study testing anticoagulant equivalency in all claimed specimen

type/anticoagulant combinations using clinical specimens that are representative of the intended use population of the device.

(H) Analytic sensitivity data using a dilution panel created from clinical samples.

(I) Analytical specificity data, including interference and cross-contamination.

(J) Device stability data, including real-time stability of reagents under various storage times and temperatures.

(K) For devices that include polyclonal antibodies, Fluorescence Minus One (FMO) studies to evaluate non-specific binding for all polyclonal antibodies. Each FMO tube is compared to reagent reference to demonstrate that no additional population appears when one marker is absent. Pre-specified acceptance criteria must be provided and followed.

(L) For devices indicated for use as-a semi-quantitative test, linearity data using a dilution panel created from clinical samples.

(M) For devices indicated for use as a semi-quantitative test, clinically relevant analytical sensitivity data, including limit of blank, limit of detection, and limit of quantification.

- iv. Identification of risk mitigation elements used by the device, including a detailed description of all additional procedures, methods, and practices incorporated into the instructions for use that mitigate risks associated with testing the device.
2. The 21 CFR 809.10 compliant labeling must include the following:
 - i. The intended use statement in the 21 CFR 809.10(a)(2) and 21 CFR 809.10(b)(2) compliant labeling must include a statement that the results should be interpreted by a pathologist or equivalent professional in conjunction with other clinical and laboratory findings. The intended use statement must also include information on what the device detects and measures, whether the device is qualitative, semi-quantitative, and/or quantitative, the clinical indications for which the device is to be used, and the specific population(s) for which the device is intended.
 - ii. A detailed description of the performance studies conducted to comply with paragraph (1)(iii) and a summary of the results.
 3. As part of the risk management activities performed under 21 CFR 820.30 design controls, product labeling and instruction manuals should include clear examples of all expected phenotypic patterns and gating strategies using well-defined clinical samples representative of both abnormal and normal cellular populations. These samples must be selected based upon the indications described in paragraph (1)(i) of this section.

This device is subject to the premarket notification requirements under section 510(k) of the FD&C Act. Thus, persons who intend to market this device type must submit a premarket notification containing information on the Flow Cytometric Test System for Hematopoietic Neoplasms they intend to market prior to marketing the device and receive clearance to market from FDA prior to marketing the device.

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 Parts 801 and 809); 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 Jacqueline Cleary at jacqueline.cleary@fda.hhs.gov or (240) 402-0490.

Sincerely,

Kelly S. Oliner, PhD
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For
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