



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center - WO66-G609
Silver Spring, MD 20993-0002

B·R·A·H·M·S GmbH, part of Thermo Fisher Scientific
C/O Bernhard Ciommer, PhD
Director Global RA and QA Compliance
Neuendorfstr. 25
16761 Hennigsdorf
Germany

February 20, 2016

Re: DEN150009
B·R·A·H·M·S PCT sensitive KRYPTOR®
Evaluation of Automatic Class III Designation – *De Novo* Request
Regulation Number: 21 CFR 866.3215
Regulation Name: Device to detect and measure non-microbial analyte(s) in human clinical specimens to aid in assessment of patients with suspected sepsis
Regulatory Classification: Class II
Product Code: PMT
Dated: February 27, 2015
Received: March 4, 2015

Dear Dr. Ciommer:

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 B·R·A·H·M·S PCT sensitive KRYPTOR, a prescription device. The indications for use of the B·R·A·H·M·S PCT sensitive KRYPTOR is:

The B·R·A·H·M·S PCT sensitive KRYPTOR is an immunofluorescent assay using Time-Resolved Amplified Cryptate Emission (TRACE) technology to determine the concentration of PCT (procalcitonin) in human serum and EDTA or heparin plasma.

The B·R·A·H·M·S PCT sensitive KRYPTOR is intended to be performed on the B·R·A·H·M·S KRYPTOR analyzer family.

The B·R·A·H·M·S PCT sensitive KRYPTOR is intended for use in conjunction with other laboratory findings and clinical assessments to aid in the risk assessment of critically ill patients on their first day of Intensive Care Unit (ICU) admission for progression to severe sepsis and septic shock.

The B·R·A·H·M·S PCT sensitive KRYPTOR is also intended for use to determine the change in PCT level over time as an aid in assessing the cumulative 28-day risk of all-cause mortality in conjunction with other laboratory findings and clinical assessments for patients diagnosed

with severe sepsis or septic shock in the ICU or when obtained in the emergency department or other medical wards prior to ICU admission.

Procalcitonin (PCT) is a biomarker associated with the inflammatory response to bacterial infection that aids in the risk assessment of critically ill patients on their first day of Intensive Care Unit (ICU) admission for progression to severe sepsis and septic shock. The percent change in PCT level over time also aids in the prediction of cumulative 28-day mortality in patients with severe sepsis and septic shock.

PCT level on the first day of ICU admission above 2.0 µg/L is associated with a higher risk for progression to severe sepsis and/or septic shock than a PCT level below 0.5 µg/L.

A PCT level that declines $\leq 80\%$ from the day that severe sepsis or septic shock was clinically diagnosed (Day 0) to four days after clinical diagnosis (Day 4) is associated with higher cumulative 28-day risk of all-cause mortality than a decline $> 80\%$.

The combination of the PCT level (≤ 2.0 ug/L or > 2.0 µg/L) at initial diagnosis of severe sepsis or septic shock with the patient's clinical course and the change in PCT level over time until Day 4 provides important additional information about the mortality risk.

The PCT level on Day 1 (the day after severe sepsis or septic shock is first clinically diagnosed) can be used to calculate the percent change in PCT level at Day 4 if the Day 0 measurement is unavailable.

FDA concludes that this device, and substantially equivalent devices of this generic type, should be classified into class II. This order, therefore, classifies the B·R·A·H·M·S PCT sensitive KRYPTOR, and substantially equivalent devices of this generic type, into class II under the generic name, "Device to detect and measure non-microbial analyte(s) in human clinical specimens to aid in assessment of patients with suspected sepsis."

FDA identifies this generic type of device as: Device to detect and measure non-microbial analyte(s) in human clinical specimens to aid in assessment of patients with suspected sepsis.

A device to detect and measure non-microbial analyte(s) in human clinical specimens to aid in assessment of patients with suspected sepsis is identified as an in vitro device intended for the detection and qualitative and/or quantitative measurement of one or more non-microbial analytes in human clinical specimens to aid in the assessment of patients with suspected sepsis when used in conjunction with clinical signs and symptoms and other clinical and laboratory findings.

Section 513(f)(2) of the Food, Drug & Cosmetic Act (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 FD&C 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 FD&C

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 FD&C 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 March 4, 2015, FDA received your *de novo* request for classification of the B·R·A·H·M·S PCT sensitive KRYPTOR. The petition was submitted under section 513(f)(2) of the FD&C Act. In order to classify the B·R·A·H·M·S PCT sensitive KRYPTOR 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 B·R·A·H·M·S PCT sensitive KRYPTOR indicated for use as follows

The B·R·A·H·M·S PCT sensitive KRYPTOR is an immunofluorescent assay using Time-Resolved Amplified Cryptate Emission (TRACE) technology to determine the concentration of PCT (procalcitonin) in human serum and EDTA or heparin plasma.

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The B·R·A·H·M·S PCT sensitive KRYPTOR is also intended for use to determine the change in PCT level over time as an aid in assessing the cumulative 28-day risk of all-cause mortality in conjunction with other laboratory findings and clinical assessments for patients diagnosed with severe sepsis or septic shock in the ICU or when obtained in the emergency department or other medical wards prior to ICU admission.

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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, including the design controls under 21 CFR part 820, provide reasonable assurance of the safety and effectiveness of the device type.

Table – Identified Risks and Required Mitigations

Identified Risks to Health	Required Mitigations
Incorrect determination of PCT value, including false positives and false negatives, by the device can lead to improper patient management	Special Controls (2), (3), (7)
Incorrect interpretation of device results by end user can lead to improper patient management	Special Controls (1), (4), (5), (6), (7)
Manual Calculation error of final results	Special Control (7)

In combination with the general controls of the FD&C Act, a device to detect and measure non-microbial analyte(s) in human clinical specimens to aid in assessment of patients with suspected sepsis is subject to the following special controls:

- 1) Premarket notification submissions must include the device’s detailed Indications for Use statement describing what the device detects and measures, the results provided to the user, whether the measure is qualitative and/or quantitative, the clinical indications for which the test is to be used, and the specific population(s) for which the device use is intended.
- 2) Premarket notification submissions must include detailed documentation of the device description, including (as applicable), all device components, software, ancillary reagents required but not provided, explanation of the device principle and methodology, and for molecular devices include detailed documentation of the primer/probe sequence, design, and rationale for sequence selection.
- 3) Premarket notification submissions must include detailed documentation of applicable analytical studies, such as, analytical sensitivity (Limit of Detection, Limit of Blank, and Limit of Quantitation), precision, reproducibility, analytical measuring range, interference, cross reactivity, and specimen stability.

- 4) Premarket notification submissions must include detailed documentation of a prospective clinical study or, if appropriate, results from an equivalent sample set. This detailed documentation must include the following information:
 - a. Results must demonstrate adequate device performance relative to a well-accepted comparator.
 - b. Clinical sample results must demonstrate consistency of device output throughout the device measuring range likely to be encountered in the Intended Use population.
 - c. Clinical study documentation must include the original study protocol (including predefined statistical analysis plan), study report documenting support for the Indications for Use(s), and results of all statistical analyses.
- 5) Premarket notification submissions must include evaluation of the level of the non-microbial analyte in asymptomatic patients with demographic characteristics (e.g., age, racial, ethnic, and gender distribution) similar to the Intended Use population.
- 6) As part of the risk management activities performed under 21 CFR 820.30 design controls, you must document an appropriate end user device training program that will be offered as part of your efforts to mitigate the risk of failure to correctly operate the instrument.
- 7) A detailed explanation of the interpretation of results and acceptance criteria must be included in the device's 21 CFR 809.10(b)(9) compliant labeling, and a detailed explanation of the interpretation of the limitations of the samples (e.g., collected on day of diagnosis) must be included in the device's 21 CFR 809.10(b)(10) compliant labeling.

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 a 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 device to detect and measure non-microbial analyte(s) in human clinical specimens to aid in assessment of patients with suspected sepsis 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 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 Yvonne Shea at 301-796-0576.

Sincerely yours,

Uwe Scherf -S

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