DE NOVO CLASSIFICATION REQUEST FOR TERRAGENE BIONOVA PHOTON BIOLOGICAL INDICATOR (BT225); TERRAGENE BIONOVA PHOTON AUTO-READER INCUBATOR (BPH)

REGULATORY INFORMATION

FDA identifies this generic type of device as:

> **Biological sterilization indicator with indirect growth detection**. A biological sterilization indicator with indirect growth detection capabilities is a device intended for use by a healthcare provider to accompany products being sterilized through a sterilization process to monitor the adequacy of sterilization. Detection of surviving microorganisms is accomplished by a method other than direct detection of growth or growth products.

NEW REGULATION NUMBER: 21 CFR 880.2806

CLASSIFICATION: Class II

PRODUCT CODE: QVB

BACKGROUND

DEVICE NAME: Terragene Bionova Photon Biological Indicator (BT225); Terragene Bionova Photon Auto-Reader Incubator (BPH)

SUBMISSION NUMBER: DEN220042

DATE DE NOVO RECEIVED: July 01, 2022

SPONSOR INFORMATION:

Terragene SA
Ruta Nacional No. 9
Km 280, Parque Industrial Micropi
Alvear, Santa Fe
Argentina

INDICATIONS FOR USE

The Terragene Bionova Photon Biological Indicator (BT225); Terragene Bionova Photon Auto-Reader Incubator (BPH) is indicated as follows:

> Terragene® Bionova® Photon Biological Indicator (BT225) is a 7-second readout Self-Contained Biological Indicator (SCBI) inoculated with a minimum of 10^6 viable *Geobacillus stearothermophilus* bacterial spores and is intended for routine monitoring of

the efficacy of steam sterilization processes. BT225 SCBI is not recommended and should not be used for qualification testing purposes. On each Terragene® Bionova® SCBI is a chemical process indicator that changes color from pink to brown when exposed to steam.

- Gravity-displacement Steam Sterilization Cycles
132 ºC, 25 minutes
132 ºC, 15 minutes
132 ºC, 10 minutes
135 ºC, 10 minutes

- Dynamic-air-removal Steam Sterilization Cycles
132 ºC, 4 minutes
135 ºC, 3 minutes

Terragene® Bionova® Photon Auto-reader Incubator (BPH) incubates at 60 °C and reads the Terragene® Bionova® Photon SCBIs at the times prescribed in the User Manual.

LIMITATIONS

Terragene Bionova Photon Biological Indicator (BT225); Terragene Bionova Photon Auto-Reader Incubator (BPH) is intended to be marketed for Over-the-Counter (OTC) device.

PLEASE REFER TO THE LABELING FOR A COMPLETE LIST OF WARNINGS, PRECAUTIONS AND CONTRAINDICATIONS.

DEVICE DESCRIPTION

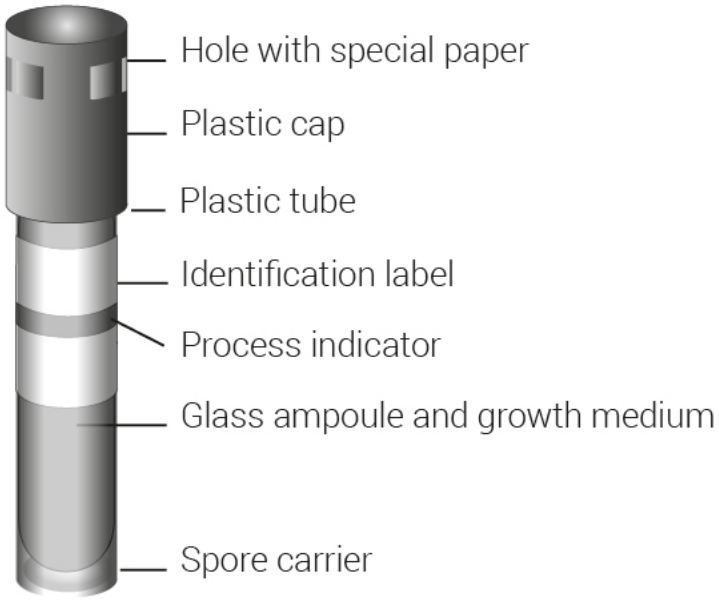
Terragene® Bionova® Photon Biological Indicator (BT225)

Terragene® Bionova® Photon Biological Indicator (BT225) is a Biological Indicator for monitoring gravity-displacement and dynamic-air-removal steam sterilization cycles at 132 ºC - 135 ºC. When BT225 is used in conjunction with the Terragene® Bionova® Photon Auto-reader Incubator (BPH), it provides a final fluorescent result at 7 seconds.

Terragene® Bionova® Photon Biological Indicators (BT225) are single-use Self-Contained Biological Indicators (SCBIs) that are formed by a carrier with *Geobacillus stearothermophilus* ATCC 7953 spores and an ampoule containing a bacteriological growth medium. Both, the media ampoule and the carrier, are contained in a polypropylene tube enclosed with a black cap with holes and a barrier permeable to steam.

Each SCBI has a label located on the outside of the tube. This label contains information regarding the expiration date and the lot of the SCBI, as well as a chemical process indicator that turns from pink to brown to indicate that the SCBI has been exposed to steam.

Basic Design



Terragene® Bionova® BPH Photon Instant Auto-reader Incubator

Terragene® Bionova® Photon Auto-reader Incubator (BPH) has been designed for the incubation at 60 ºC and automatic readout of the Bionova® Photon line of Self-contained Biological Indicators (SCBIs) appropriate for monitoring steam sterilization cycles. It allows an instant readout (7-second) of the BT225 SCBI using fluorescence technology and 48-hour incubation for visual color change confirmation.

Usage: For incubation and readout of Bionova Instant BT225 SCBIs. Readout fluorescence system after 7-second incubation at 60 °C.

SUMMARY OF BENCH STUDIES

SHELF LIFE/STERILITY

The Terragene® Bionova® Photon Biological Indicator is a single-use device with 18 months of shelf life which is supported by validation testing.

Chemical Process Indicator on SCBI label has an expiration date of 18 months when used as part of SCBI. End Point Stability Reaction: chemical indicator endpoint shall remain unchanged for a period.
of not less than 6 months when stored at previously indicated conditions.

Terragene® Bionova® BPH Photon Instant Auto-reader Incubator shelf life is 5 years.

BIOCOMPATIBILITY/MATERIALS

The Terragene® Bionova® Photon Biological Indicator (BT225) has no patient contacting components/materials. The sponsor provided material certification statement as per Attachment F of the FDA 2020 Biocompatibility Guidance document, *Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process,"* found at https://www.fda.gov/media/142959/download

SOFTWARE

The Terragene® Bionova® BPH Photon Instant Auto-reader Incubator software has the functionality of controlling the equipment user interface through a panel (with LEDs and push buttons) allowing its configuration. The software is able to control the incubation temperature, fluorescence readout process for biological indicators by UV-excitation and subsequent readout

of the emitted light using photodiodes. The software testing was conducted as per FDA guidance document, "*Content of premarket submissions for Device Software Functions,"* found at *https://www.fda.gov/media/153781/download*. The software validation and verification include the software description, level of concern (LOC), Device hazard analysis, software requirements/design specifications, Architecture design chart, software development and maintenance activities, Unresolved anomalies (Bugs and Defects), Revision level, History, Cybersecurity analysis, Traceability analysis/matrix and validation testing. The verification and validation testing reports are found adequate. The software is an accessory to the subject device for the reader/incubator and of a moderate level of concern.

ELECTROMAGNETIC CAPABILITY & ELECTROMAGNETIC SAFETY

Electrical safety and electromagnetic compatibility for Terragene® Bionova® BPH Photon Instant Auto-reader Incubator was demonstrated following IEC 61010-1 for electrical safety, IEC 61010-2-010 CB certificate, ANSI C63.27 2017 Wireless Coexistence Report, IEC 61326-1, Electrical equipment for measurement, control and laboratory use-EMC requirements-Part 1: General requirements. The electrical safety and electromagnetic compatibility test reports are found to be adequate to support the functionality of Terragene® Bionova® BPH Photon Instant Auto-reader Incubator.

PERFORMANCE TESTING - BENCH

The following performance tests support that the device can achieve its intended use:

- **In-Use Performance Testing for Bionova Photon Biological Indicator (BT225)**

  The study demonstrated correct performance of Bionova Photon Biological Indicator (BT225) for claimed gravity-displacement and dynamic-air-removal sterilization cycles when subjected to in-use testing in health-care facilities steam sterilizers and read at 7-second (fluorescence) and 48-hour (visual). All results including positive controls met the acceptance criteria.

- **Design and Performance Validation Bionova® Photon Biological Indicator (BT225)**

  The validation testing and the associated validation test reports consisted of different test protocols to support design and performance of the subject device, as described below:

- Viable spore population assay for Bionova® BT225 Instant Readout Biological Indicators
  The purpose of this study is to demonstrate that the subject device meets specifications for spore population according to ANSI/AAMI ISO 11138-1, ANSI/AAMI ISO 11138-3 standards and the FDA guidance, *Biological Indicator (BI) Premarket Notification [510(k)] Submissions,* found at https://www.fda.gov/media/71134/download. Three lots were evaluated and all three lots met the specifications.

- Resistance characteristics study for Bionova® BT225 Instant Readout Biological Indicators
  The purpose of this study is to evaluate the resistance characteristics (1) D-value, 2) Z-value, 3) Survival Time, and 3) Kill Time) of the subject device. All the samples met specifications for resistance characteristics of the "Recommended Minimum Populations and Resistance Characteristics" stated on the FDA guidance for BIs, as well as comply with ANSI/AAMI ISO 11138-1:2017 and ANSI/AAMI ISO 11138-3:2017 standards.

- Recovery medium test for Bionova® BT225 Instant Readout Biological Indicators.
  The purpose of this study was to demonstrate the suitability of the culture medium used in the build-up of the subject device. Culture medium was evaluated from three different lots used in the build-up of the subject device. The results support spore recovery after steam sterilization process, complying with ANSI/AAMI ISO 11138-1 standard (Sub-clause 7.2).

- Carrier and primary packaging materials evaluation for Bionova® BT225 Instant Readout Biological Indicators.
  The purpose of this study was to evaluate the impact of carriers and primary packaging materials on the performance of BIs. The subject device was tested according to the methods described in the FDA special controls guidance for BIs. The results demonstrate compliance with ANSI/AAMI ISO 11138-1:2017 standard.

- Reduced Incubation Time for Bionova® BT225 Instant Readout Biological Indicators.
  The 7-second reduced incubation time for the subject device was validated for 7-second readout, 48-hours, and 7-days. In all cases, tests carried out showed appropriate sensitivity value above 97% and specificity value above 87.5%.

- Visual readout stability for Bionova® BT225 Instant Readout Biological Indicators.
  The purpose of this study was to evaluate the color stability for 7-days of incubation for different lots of BIs. Visual inspection of the culture medium for 7 days confirms its color stability for lethal and non-lethal cycles. Culture medium color is stable during 7 days of incubation.

- Holding time assessment for Bionova® BT225 Instant Readout Biological Indicators.
  The purpose of this study was to validate the claimed 7-day holding time between sterilization and incubation. The tests carried out showed a sensitivity value above 97% indicating that there is no difference in the results obtained for the declared 7-day holding time. Results were also evaluated for the 7-second fluorescence readout, 48-hour visual readout, 7-day readout, and 14-day readout. The results for all incubation periods and readout methods were equivalent.

- Bionova® BT225 Instant Readout Biological Indicators limit of detection.
  The purpose of this study was to show that the incubator can detect a very low number of viable spores (i.e. 1-100 spores). Fluorescence readouts were compared with the plating results, positive fluorescence readouts were obtained for every BI which showed 1 to 100 viable count result. This demonstrates the incubator can detect a very low number of

viable spores and the limit of detection is good enough to guarantee the product sensitivity. The detection limit (LOD), LOQ, sensitivity and specificity testing methodology are expected to be clearly described and are justified against appropriate worst-case detection conditions and aligned with the FDA recognized standard, such as CLSI EP 17-A2 (Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline-Second Edition).

- Shelflife stability study for Bionova® BT225 Instant Readout Biological Indicators. Three different lots of SCBIs were evaluated for stability via real-time aging for 18 months. Samples from each lot were evaluated in accordance with ANSI/AAMI ISO 11138-1:2017 and ANSI/AAMI ISO 11138-3:2017 for the spore population stability and D-value. All samples met the acceptance criteria of those standards for all time points.

- **Design and Performance Validation BT225 Chemical Indicator**

  The purpose of this study is to validate the performance of chemical process indicator on subject device label according to ANSI/AAMI ISO 11140-1 standard and in compliance with FDA guidance for CIs, Premarket Notification submissions for chemical indicators, www.fda.gov/media/72010/download. The results of this study show that all samples met the acceptance criteria for the testing conditions. These results were also verified for samples that had been real-time aged for 18-24 months. The results for aged and fresh samples were equivalent. Another test was conducted to evaluate samples aged throughout the 18-month claimed shelf-life. Another study was conducted to verify that the chemical indicator labels do not offset or transfer when in contact with the same substrate from which they are manufactured. The result show that the indicators do not release any substance or bleed when they come in contact with their substrate.

The sponsor completed testing and demonstrated that the Terragene Bionova® performance complies with the standards. The device has been appropriately evaluated for performance on the bench.

LABELING

The labeling consists of Instructions for Use in user guide and packaging labels of the device.

RISKS TO HEALTH

The table below identifies the risks to health that may be associated with use of biological sterilization indicator with indirect growth detection and the measures necessary to mitigate these risks.

Identified Risks to Health and Mitigation Measures

Risks to Health	Mitigation Measures
Infection resulting from false negative results for inadequately sterilized devices	Non-clinical performance testing Software verification, validation, and hazard analysis Labeling
Delayed or cancelled procedure due to false positive results	Non-clinical performance testing Software verification, validation, and hazard analysis Labeling
Electrical shock or interference with other devices	Electrical safety testing Electromagnetic compatibility testing
False positive or false negative results due to device degradation in-storage	Shelf-life testing
Inability to detect growth or growth products due to inadequate incubation conditions, resulting in false negative result.	Non-clinical performance testing

SPECIAL CONTROLS

In combination with the general controls of the FD&C Act, the biological sterilization indicator with indirect growth detection is subject to the following special controls:

(1) Non-clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use and must include the following:
   (i) Demonstration that the measured response is dependent on the sterilization cycle parameter(s) representing the indicated cycle conditions;
   (ii) Analytical performance characteristics validation, including scientifically justified samples, worst case conditions, test protocols, reports, and data analysis to evaluate the indicated cycle conditions with established acceptance criteria for each parameter;
   (iii) Comparison of detected signal with the number of surviving spores using objective performance measures with both sensitivity and specificity parameters.);
   (iv) Limit of detection testing;
   (v) End point color stability testing; and
   (vi) Validation of accuracy over a specified readout time.

(2) Performance data must support the shelf life of the device by demonstrating continued device functionality over the labeled shelf life.

(3) Software verification, validation, and hazard analysis must be performed for any software components of the device.

(4) Performance data must demonstrate the electromagnetic compatibility (EMC) and electrical safety of the electrical components of the device.

(5) Labeling must include:
    (i) Information on the sensitivity and specificity of the device and warning/precaution statements for any potential false positive or false negative rates;
    (ii) Time interval for read out; and
    (iii) For devices intended for use in process monitoring only, warnings against use for cycle qualification.

BENEFIT-RISK DETERMINATION

Benefit

The sponsor demonstrated that the probable benefits include the following:

*The benefits of the device are based on nonclinical laboratory studies described above. Testing demonstrated low level of detection by incubator/auto reader to detect minimum number of spores leading to increased sensitivity >97% and improved sterilization process monitoring.

*The shorter biological indicator read time will make sterilized device distribution faster to support patient procedures as well as clinical laboratory experiments / studies.

Risk

The risks of the device are based on nonclinical laboratory testing described above.

The main probable risks of the proposed device are a false negative result leading to ineffective sterilization of medical devices or a false positive result leading to the requirement to re-run the sterilization cycle, causing delayed procedures or degradation of the components being sterilized. The testing demonstrated >97% sensitivity and therefore supported routine monitoring of the efficacy of steam sterilization processes. Specificity testing did not achieve the >95% threshold, therefore the device is not recommended and should not be used for qualification testing purposes. There is an additional risk of electrical shock and interference with other devices.

The device ultimately did not pose a direct risk to patients and identified risks have been mitigated with appropriate performance testing and warning/precaution statements in the device labeling/instructions for use and special controls.

Based on the performance testing provided (in particular; sensitivity, specificity, end point stability, shelf life, software validation and labeling) and risk mitigations, the probable benefits outweigh the probable risks for the subject device.

Patient Perspectives

This submission did not include specific information on patient perspectives for this device.

Benefit/Risk Conclusion

In conclusion, given the testing provided and available information above, for the following indication statement:

> Terragene® Bionova® Photon Biological Indicator (BT225) is a 7-second readout Self-Contained Biological Indicator (SCBI) inoculated with a minimum of 10^6 viable *Geobacillus stearothermophilus* bacterial spores and is intended for routine monitoring of the efficacy of steam sterilization processes. BT225 SCBI is not recommended and should not be used for qualification testing purposes. On each Terragene® Bionova® SCBI is a chemical process indicator that changes color from pink to brown when exposed to steam.
> - Gravity-displacement Steam Sterilization Cycles
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> - Dynamic-air-removal Steam Sterilization Cycles
> 132 ºC, 4 minutes
> 135 ºC, 3 minutes
>
> Terragene® Bionova® Photon Auto-reader Incubator (BPH) incubates at 60 °C and reads the Terragene® Bionova® Photon SCBIs at the times prescribed in the User Manual.

The probable benefits outweigh the probable risks for the Terragene Bionova Photon Biological Indicator (BT225); Terragene Bionova Photon Auto-Reader Incubator (BPH). The device provides benefits, and the risks can be mitigated by the use of general controls and the identified special controls.

CONCLUSION

The De Novo request for the Terragene Bionova Photon Biological Indicator (BT225); Terragene Bionova Photon Auto-Reader Incubator (BPH) is granted, and the device is classified as follows:

> Product Code: QVB
> Device Type: Biological sterilization indicator with indirect growth detection
> Regulation Number: 21 CFR 880.2806
> Class: II