December 23, 2020

Helix OpCo, LLC
Gloria Lee, Ph.D.
Senior Director Regulatory Affairs
96 Colbeck Street
Toronto, Ontario M6S1 V2
Canada

Re: DEN190035
Trade/Device Name: Helix Laboratory Platform
Regulation Number: 21 CFR 866.6000
Regulation Name: Whole exome sequencing constituent device
Regulatory Class: Class II
Product Code: QNC
Dated: July 31, 2019
Received: August 2, 2019

Dear Gloria Lee:

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 Helix Laboratory Platform, a prescription device with the following indications for use:

> The Helix Laboratory Platform is a qualitative in vitro diagnostic device intended for exome sequencing and detection of single nucleotide variants (SNVs) and small insertions and deletions (indels) in human genomic DNA extracted from saliva samples collected with Oragene® Dx OGD-610. The Helix Laboratory Platform is only intended for use with other devices that are germline assays authorized by FDA for use with this device. The device is performed at the Helix laboratory in San Diego, CA.

Although this letter refers to your product as a device, please be aware that some granted products may instead be combination products. If you have questions on whether your product is a combination product, contact CDRHProductJurisdiction@fda.hhs.gov. FDA concludes that this device should be classified into Class II. This order, therefore, classifies the Helix Laboratory Platform, and substantially equivalent devices of this generic type, into Class II under the generic name Whole Exome Sequencing Constituent Device.

FDA identifies this generic type of device as:

> **Whole Exome Sequencing Constituent Device**. A whole exome sequencing constituent device is for germline whole exome sequencing of genomic deoxyribonucleic acid (DNA) isolated from human specimens. The DNA sequence generated by this device is intended as input for clinical

germline DNA assays that have FDA marketing authorization and are intended for use with this device.

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 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 request FDA to make a risk-based classification of the device under section 513(a)(1) of the Act. On December 13, 2016, the 21st Century Cures Act removed a requirement that a De Novo request be submitted within 30 days of receiving an NSE determination. 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 announcing the classification.

On August 2, 2019, FDA received your De Novo requesting classification of the Helix Laboratory Platform. The request was submitted under section 513(f)(2) of the FD&C Act. In order to classify the Helix Laboratory Platform 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 and in submission supplements (Q160402/S012, S013, S014, S015, S016, S017) and via interactive email, FDA has determined that, for the previously stated indications for use, the Helix Laboratory Platform 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 mitigation measures associated with the device type are summarized in the following table:

Table 1 – Identified Risks to Health and Identified Mitigations

Identified Risks to Health	Mitigation Measures
Inaccurate test results and failure to provide results	Certain design verification and validation, including certain analytical studies and clinical studies. Certain labeling information, including certain performance information and device limitations.
Incorrect application or interpretation of results	Certain design verification and validation, including certain clinical studies. Certain labeling information, including certain performance information and device limitations.
User error and improper use of the device	Certain design verification and validation, including certain analytical studies and clinical studies. Certain labeling information, including certain performance information and device limitations.

In combination with the general controls of the FD&C Act, the whole exome sequencing constituent device is subject to the following special controls:

(1) The intended use on the device's label and labeling required under 21 CFR 809.10 must include:

i. The indicated variant types for which acceptable, as determined by FDA, validation data has been provided. Distinct variant types are considered as single nucleotide variant, insertion, deletion, tandem repeats, copy number variants, or gene rearrangements, and validated for specific sizes and lengths, as applicable.

ii. The indicated specimen type(s) for which acceptable, as determined by FDA, validation data has been provided.

(2) The labeling required under 21 CFR 809.10(b) must include:

i. The identification of, or the specifications for, the collection device or devices to be used for sample collection, as applicable.

ii. A description of the reportable range, which is the region of the genome for which the assay is intended to provide results, as well as a description of the targeted regions of the genome that have enhanced coverage. This must include a description of any genomic regions that are excluded from the reportable region due to unacceptable risk of erroneous results, or for other reasons. A description of the clinically relevant genes excluded from the reportable range must also be included, if applicable.

iii. A description of the design features and control elements, including the quality metrics and thresholds which are used for reporting the analytical range (the genomic DNA in the reportable range that passed the quality metrics in the run required for reporting to the user) that are incorporated into the testing procedure, that mitigate the risk of incorrect clinical results. The following metrics are considered applicable in the generation of high confidence data and the established thresholds for these metrics for reporting must be described and be determined to be acceptable by FDA: cluster density and percent of cluster pass quality filter, percent of bases meeting the minimum base quality score, average coverage of reads, percent of reads mapped on target, percent of reportable region with coverage meeting the minimum requirement, percent of unassigned read indices, percent of reads for non-human DNA, allele fraction, and strand bias. Any alternate metrics used must be described and an acceptable, as determined by FDA, rationale for applicability must be provided.

iv. A representative sample of the device output report(s) provided to users, which must include any relevant limitations of the device, as determined applicable by the FDA.

(3) Design verification and validation must include:

i) A detailed description of the impact of any software, including software applications and hardware-based devices that incorporate software, on the device's function.

ii) Acceptable data, as determined by FDA, demonstrating how the key quality metrics and quality metric thresholds in the list in paragraph (b)(2)(iii) for reporting were established and optimized for accuracy using appropriate DNA standards with established reference genomic sequence. Data must include, as applicable, base quality score, allele fraction for heterozygosity and coverage, and other applicable metrics.

iii) Data demonstrating acceptable, as determined by FDA, analytical device performance using patient specimens representing the full spectrum of expected variant types reported across the genome and in genomic regions that are difficult to sequence. The number of specimens tested must be sufficient to obtain estimates of device performance that are representative of the device performance that can be expected for the reportable region and clinically relevant subsets of the reportable region, as applicable. For each study, data must include a summary of the key quality metric data; the number and percentage of true positives (TP), false positives (FP), and false negatives (FN); number and percentage of no-calls; positive percent agreement (PPA); negative percent agreement (NPA); positive predictive value (PPV); technical positive percent value (TPPV); and non-reference concordance (NRC). These data must be provided per sample and stratified by variant type. The variant data must also be further stratified by size and zygosity (homozygous common allele, heterozygous, homozygous rare allele). Data demonstrating the accuracy assay based on guanine and cytosine (GC) content, pseudogenes, and proximity to short tandem repeats must also be presented. The data must be presented for the entire exome and also for clinically relevant subsets of the reportable region. For each study, the number of run failures and repeat/requeued specimens must be summarized.

iv) Documentation of acceptance criteria that are applied to analytical and clinical validation studies, which must be justified based on the estimated risk of erroneous results on clinically significant genes and variants and must be clinically acceptable, as determined by FDA. The acceptance criteria must be pre-specified prior to clinical and analytical validation studies, and all validation testing results must be documented with respect to those acceptance criteria.

v) Analytical validation must be demonstrated by conducting studies that provide:

   A. Data demonstrating acceptable, as determined by FDA, accuracy based on agreement with an acceptable, as determined by FDA, comparator method(s) that has been validated to have high accuracy and reproducibility. Accuracy of the test shall be evaluated with reference standards and clinical specimens for each indicated specimen type of a number determined acceptable by FDA, collected and processed in a manner consistent with the test's instructions for use.

   B. Data demonstrating acceptable, as determined by FDA, precision from a precision study using clinical samples to adequately evaluate intra-run, inter-run, and total

variability across operator, instrument, lot, day, and site, as applicable. The samples must include the indicated range of DNA input. Precision, including repeatability and reproducibility, must be assessed by agreement between replicates, and also supported by sequencing quality metrics for targeted regions across the panel. Precision must be demonstrated per specimen and in aggregate. Precision data must be calculated and presented with and without no calls/invalid results.

C. Data demonstrating acceptable, as determined by FDA, accuracy in the presence of clinically relevant levels of potential interfering substances that are present in the specimen type and intended use population, including, for example, endogenous substances, exogenous substances, and microbes, as applicable.

D. Data demonstrating the absence of sample cross contamination due to index swapping (misassignment).

E. Data demonstrating that the pre-analytical steps such as DNA extraction are robust such that sources of variability in these steps and procedures do not diminish the accuracy and precision of the device.

F. Data demonstrating that acceptable, as determined by FDA, device performance is maintained across the range of claimed DNA input concentrations for the assay.

vi) Design verification and validation for software within the whole exome sequencing constituent device must include the following:

A. Detailed description of the software, including specifications and requirements for the format of data input and output, such that users can determine if the device conforms to user needs and intended uses.

B. Device design must include a detailed strategy to ensure cybersecurity risks that could lead to loss of genetic data security, are adequately addressed and mitigated (including device interface specifications and how safe reporting of the genetic test is maintained when software is updated). Verification and validation must include security testing to demonstrate effectiveness of the associated controls.

C. Device design must ensure that a record of critical events, including a record of all genetic test orders using the whole exome sequencing constituent device, device malfunctions, and associated acknowledgments, is stored and accessible for an adequate period to allow for auditing of communications between the whole exome sequencing constituent device and downstream clinical genetic tests, and to facilitate the sharing of pertinent information with the responsible parties for those devices.

vii) A protocol reviewed and determined acceptable by FDA, that specifies the verification and validation activities that will be performed for anticipated bioinformatic software modifications to reevaluate performance claims or performance specifications. This protocol

must include a process for assessing whether a modification to the bioinformatics software could significantly affect the safety or effectiveness of the device. The protocol must include assessment metrics, acceptance criteria, and analytical methods for the performance testing of changes, as applicable. The protocol must also include the process for communicating to developers of downstream clinical genetic tests the impact of the bioinformatics software change on the whole exome sequencing constituent system genetic data output so they may implement appropriate corresponding actions.

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 whole exome sequencing constituent device they intend to market 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) for devices or postmarketing safety reporting (21 CFR 4, Subpart B) for combination products (see https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR 4, Subpart A) for combination products; 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.

For comprehensive regulatory information about medical devices and radiation-emitting products, please see Device Advice (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance) and CDRH Learn (https://www.fda.gov/training-and-continuing-education/cdrh-learn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

If you have any questions concerning the contents of the letter, please contact Donna Roscoe at Donna.Roscoe@fda.hhs.gov or Wenming Xiao at Wenming.Xiao@fda.hhs.gov.

Sincerely,

Reena Philip -S

Reena Philip, Ph.D.
Director
Division of Molecular Genetics and Pathology
OHT7: Office of In Vitro Diagnostics
and Radiological Health
Office of Product Evaluation and Quality
Center for Devices and Radiological Health