K232613
Innolitics, LLC
Trade/Device Name: CT Cardiomegaly (v.1.0.0)
Contact Name: Meritxell Martinez

This document is being communicated via e-mail as an attachment. The date on which FDA sent this e-mail is the official date of this correspondence.

We have reviewed your submission K232613 and have determined that additional information is required. Your file is being placed on hold pending a complete response to the attached deficiencies.

Please submit your response, as a complete eSTAR file, referencing the submission number K232613, electronically through the CDRH Portal. For more information on the CDRH Portal, please visit https://www.fda.gov/medical-devices/industry-medical-devices/send-and-track-medical-device-premarket-submissions-online-cdrh-portal. Your response is due within 180 days from the date of this request, which is the hold date plus 180 days. If a complete response is not sent to us through the CDRH Portal by 4 PM ET on the due date, we will consider this submission to be withdrawn, and we will delete it from our review system.

You may not market this device until you have received a letter from FDA allowing you to do so. If you market the device without FDA clearance, you will be in violation of the Federal Food, Drug, and Cosmetic Act.

If you would like a meeting or teleconference with the review team and management to discuss your planned approach for responding to the attached deficiencies, please submit your request for feedback as a Submission Issue Q-Submission (Q-Sub). Please note that a Submission Issue Q-Sub does not take the place of a formal response to this email notification. As noted above, FDA will consider this submission to be withdrawn if FDA does not receive, in a submission sent to us through the CDRH Portal by 4 PM ET on the due date, a complete response to all of the attached deficiencies.

This request for additional information has undergone supervisory review to ensure that the deficiencies cited are least burdensome and relevant to the marketing decision. Please see the revised guidance "Developing and Responding to Deficiencies in Accordance with the Least Burdensome Provisions" (https://www.fda.gov/media/71735/download) for clarification regarding major and minor deficiencies.

MAJOR DEFICIENCY LIST

The Agency has identified major deficiencies that if not adequately resolved, may preclude a favorable decision on the marketing application.

Performance Testing

1. You provided the performance testing results for your device in Section 9- Clinical Performance Assessment Results (DOC-0053_RevB). While we acknowledge that you reported the summary results for the primary and secondary end points in Sections 9.1 and 9.2, respectively, these are high level results which do not allow complete evaluation of your device performance. We have the following comments about the performance testing results:
   a. You provided the results for the Cardiothoracic Ratio and Heart to Chest Area Ratio as the Mean Difference [95% CI] and the standard deviation of differences. However, in order to evaluate the device performance with certainty, additional details on the testing results are needed. Please provide the Bland Altman plots for these measurements, specifying the limits of agreement. Additionally, you reported mean difference which may not quantify the individual (case based) measurement errors well as the positive and negative differences could average out. We recommend that you report the mean square error or the mean absolute error to adequately quantify the device performance.
   b. You provided the results for the secondary endpoints of your device in Section 9.2.2 where you provided the "Observed Dice [95% CI]". However, this summary information does not allow us to evaluate the robustness of your device performance. Please provide the distribution (histogram) of your Dice scores for us to be able to completely evaluate your device performance. Additionally, the segmentation models implemented in your device used "Dice score" as the loss function. Therefore, because of the inherent device design, the Dice scores alone do not provide sufficient assurance of segmentation performance. We recommend that you report your device performance using an additional segmentation metric such as Hausdorff distance. Please provide the results of your device performance using an additional evaluation metric such as Hausdorff distance.
   c. You provided the mean difference for Key Slice Detection in Section 9.2.1 using a prespecified criteria of mean difference target <5 mm. However, as noted elsewhere in this letter, it is not clear what the role of this "Key Slice" is in the clinical deployment of your device and how it affects the device performance. Please clarify if other performance testing results including the CTR, heart to chest area ratio and segmentation are influenced by errors in the "Key Slice" detector. If so, please provide additional information on how the Key Slice detection error impacts device performance, how the selected target of <5mm is justified and the distribution of errors (histogram) for the key slice position.
   d. We acknowledge that as part of your data sampling strategy, you provided distribution of test cases by patient demographics (age, sex, race, ethnicity), confounding conditions, and imaging characteristics (including protocol, slice thickness, scanner manufacturer, presence or absence of contrast, kVA). However, you did not provide any subgroup analysis for these factors to demonstrate the generalizability of the device performance. Please provide subgroup analysis for the factors listed above to demonstrate that the device performance is generalizable.

   Without this information, we cannot evaluate with certainty that your device performance is generalizable and demonstrates substantial equivalence to the predicate device. Please refer to Section VI of the Technical Performance Assessment of Quantitative Imaging in Radiological Device Premarket Submissions guidance (https://www.fda.gov/media/123271/download).

2. You provided information on the reference standard for the test dataset in Section 8.2 (DOC-0053_RevB_Clinical_Performance_Assessment_Report) stating that three board-certified radiologists

"*provided a segmentation for the heart and the inner chest independently from the other radiologists*". You also stated that the reference standard also involved identifying, "*the location of the Key Heart Slice*." You also provided estimates of measurement agreement in terms of ICC. However, based on the limited information provided, the exact details of how the reference standard was determined remain unclear. Please address the following comments about the reference standard:

a. It is not clear if the experts provided the Cardiothoracic Ratio (CTR) independently, in addition to the segmentation for the heart and inner chest cavity. Given that the primary output of the device is CTR, it is expected that the experts would provide their independent assessment of CTR. Please clarify if the experts provided independent measurements of CTR. Please also clarify if the area measurements were directly driven from the segmentations provided by the experts or were independently provided by the experts.

b. You noted that the experts also identify a "Key Heart Slice" for each case. However, it is not clear how the "Key Heart Slice" is defined and what instructions were provided to the experts to identify the "Key Heart Slice". Please provide information on how the "Key Heart Slice" was defined and what instructions were provided to the experts in this regard. Please also clarify how the "Key Heart Slice" selection impacts the clinical performance of the device and the performance testing results.

c. We acknowledge that you provided data on the measurement agreement between different experts in terms of ICC (Pg. 10/12, DOC-0053_RevB). Based on the information provided in the Section 10.1 (Acceptance Criteria, DOC-0052), it appears that the reference CTR measurement was based on the average of the three experts' measurements. Likewise, the Dice score results would be reported as average of Dice score between device segmentation and each expert's segmentations. Please clarify how the consensus reference standard, against which the device performance will be evaluated, was established from the independent measurements of each expert, both for the CTR and segmentation measurements. Additionally, it is not clear how the ICC was used to measure agreement on segmentation performance. In order to better interpret the inter-expert agreement, we recommend that you provide Bland Altman plots for the CTR measurements as well as some segmentation metrics (such as Dice Similarity Coefficient).

d. You noted, "*Segmentations will be created using an online annotation platform cleared by the FDA for diagnostic use. The platform allows for viewing of volumetric radiological datasets and provides tools for manually creating, editing, and reviewing segmentations*". Please provide the 510(k) number (K#) for the FDA cleared device which was used for annotation during establishment of reference standard.

This information is needed for us to evaluate with certainty that your device performance was evaluated against a robust reference standard to demonstrate that it is as safe and effective as the predicate device. Please refer to Sections V and VI of the Technical Performance Assessment of Quantitative Imaging in Radiological Device Premarket Submissions guidance (https://www.fda.gov/media/123271/download).

3. You noted, "*A diverse set of CT studies were available for training and testing CT Cardiomegaly. Data was sampled from a database curated by the University of Alabama at Birmingham of over 8,000 imaging studies from over 300 unique imaging sites*" (Pg. 5/12, Section 7, DOC-0053_RevB). You also provided the distribution of "Training+Tuning" and "Clinical Performance Assessment" datasets in Section 7.3 (Pgs. 6-8/12, DOC-0053_RevB), where the training/tuning data accounts for 1600 patients from 267 sites and test data accounts for 275 patients from 66 sites. However, it is not clear how these cases account for the 8000 imaging studies that you referred to in your original database. It is also not

clear if the test data could have multiple studies from the same patient or the results are reported for 275 unique patients. Finally, it is not clear what the geographical location of the 66 independent test sites was and how many cases were contributed by each site (275 cases from 66 sites appears to represent only about 4 cases per site). Please clarify if only 275 studies from 275 unique patients were used for the performance testing of the device and unit of analysis was patient. If multiple studies from the same patient were used in the testing, please clarify how intra-patient correlations were taken into account in your analyses. Please also provide information/distribution on how many cases each of the 66 unique sites contributed to the test data. This information is needed for us to evaluate with certainty that your data sampling and performance analysis protocol used to demonstrate substantial equivalence of your device to the predicate is adequate. Please refer to Sections V and VI of the Technical Performance Assessment of Quantitative Imaging in Radiological Device Premarket Submissions guidance (https://www.fda.gov/media/123271/download).

Device Description

4. You provided "high-level algorithm data flow diagram" in Section 7.3.1 (DOC-0040_Software_Description) and the schematic diagram for the device workflow in Section 5 (DOC-0008_System_and_Software_Architecture_Diagram.pdf). However, based on the information presented in these diagrams as well as the associated description, the workflow of your device is not clear and does not allow understanding of your device design. Specifically, we have the following comments:

a. In your flow diagram (Pg. 8/15, DOC-0040), the heart detector algorithm appears as the first processing module, before the heart segmentation and key heart slice localizer module. However, you stated in Section 7.5.1, "*The Heart Detector algorithm inputs a list of 2D axial CT slices. The algorithm uses the output of the Slice Localizer Model to select a subset of slices that contain the heart. The algorithm returns a list of all slices that are predicted to be less than 5 mm from the Key Heart Slice. If no slices are selected, then the series is rejected*". It is not clear how the "Heart Detector algorithm" functions as, based on the description above, it is dependent on the output of the "Slice Localizer Model" which appears later in the workflow (Section 7.3.1). It appears that the "Key Heart Slice" is identified as the output of the "Key Heart Slice Localizer Algorithm" which appears much later in your device workflow per the diagram in Section 7.3.1. Please clarify how the "Heart Detector algorithm" works, where it fits in the device workflow and how the "Key Heart Slice" is identified.

b. You described the "Slice Localizer Model" in Section 7.4.1, noting, "*The Slice Localizer Algorithm inputs a 2D axial CT slice. The algorithm computes an absolute distance (in mm) to the Key Heart Slice (a single slice in the CT volume where the heart area is at its maximum)*". However, per the diagram presented in Section 7.3.1, "Key Heart Slice with Heart Segmentation" is the output of the "Key Heart Slice Localizer Algorithm". It is not clear how the "Key Heart Slice Localizer Algorithm" works and computes the distance to "Key Heart Slice" which the algorithm is itself trying to identify. Moreover, you noted in Section 7.4.1 (DOC-0040), "*The algorithm uses a deep neural network using a regression network based on the VGG architecture*" and that the output of this model is "*single floating point value*". However, it is not clear what the underlying regression model (what is being regressed) is and what the "single floating point value" corresponds to. Please provide additional details on the "Key Heart Slice Localizer Algorithm", clarifying its placement in the device workflow, its input(s) and input dependencies, details on how this reference

standard/truthing/annotation for training this model is established and what the output of this algorithm is.

c. You provided illustrations for "Supplementary Information" provided in the output report (Pg. 11/21, DOC-0013_RevB_User_Manual) which includes "Coarse Detection Slices" and "Potential Key Slices". The "Potential Key Slices" also includes information as "loc: 0 cm", "loc: 0.25 cm". However, it is not clear what these "Coarse Detection Slices" and "Potential Key Slices" are, how they are identified, what is "loc" referenced to and how the users are expected to interpret and use this supplementary information. Please provide complete description of how these "Coarse" and "Potential Key Slices" are identified, how is there location information determined (and with reference to what) and how are the ends users expected to interpret and use the information provided in these slides. Additionally, it is not clear how the contours shown on these slices were validated in your performance testing.

d. You provided the architectural details of "Heart Segmentation Model" in Section 7.4.2, noting that it is based on U-net architecture and produces a 2D binary mask representing the heart and background. Based on the algorithm flow diagram in Section 7.3.1, this model needs at its input "Heart Slices" produced by the "Heart Detector Algorithm". However, as noted in part(a) of this question above, the "Heart Detector Algorithm" depends on "Key Heart Slice". Moreover, per the diagram in Section 5 of System and Software Architecture (Pg. 2/4, DOC-0008), the "ROI segmentator" appears after the "Key Slice Detector". It is not clear where the "Heart Segmentation Model" fits in the device workflow and whether all slices are segmented or only the key slice. Please also clarify how the "ROI Segmentator" referenced in DOC-0008 relates to the "Heart Segmentation Model" in Section 7.4.2 (DOC-0040).

e. You described the "*Inner Chest Segmentation Algorithm" in Section 7.4.3, noting, "The Inner Chest Segmentation algorithm inputs a 2D axial CT slice… The algorithm uses the same U-net architecture, training parameters, and hyperparameters as the Heart Segmentation Model*". However, based on this description and the diagram in Section 7.3.1, it is not clear if this chest segmentation is only performed for key heart slices or all the slices. Please clarify if each slice in the series is segmented for identifying inner chest or this algorithm is run only on some pre-selected slices. In the latter case, please provide details on the pre-selected slices as to how they are selected and their number.

This information is needed to help us understand the design and underlying functionality of your device and to determine how it should be tested to establish substantial equivalence to the predicate device. Please refer to Section VI of the Technical Performance Assessment of Quantitative Imaging in Radiological Device Premarket Submissions guidance (https://www.fda.gov/media/123271/download).

5. You provided the list of inclusion criteria for your device in Section 8.1 (DOC-0052), which includes, "*In at least one of the axial CT series, the Key Heart Slice must be within the field of view. These criteria allow for a variety of CT series that contain the heart within the field of view...*". However, it is not clear what the definition of "*Key Heart Slice*" is and how will this inclusion criterion be ensured/implemented in the real-world clinical deployment of the device as this is not a standard clinical term. Please clarify how this inclusion criterion including the definition of "Key Heart Slice" aligns with the clinical use of the subject device and how such identification of the presence or absence of "Key Heart Slice" can be ensured by the end user in real world clinical scenario. The device description and the information

provided to the end users should be in line with the device design to mitigate any risks associated with patient management and to demonstrate substantial equivalence to the predicate. Please refer to Section VI of the Technical Performance Assessment of Quantitative Imaging in Radiological Device Premarket Submissions guidance (https://www.fda.gov/media/123271/download).

6. Your device design includes default reference value of 0.5629 for "*linear-based Cardiothoracic (CTR) Index*" (Pg. 15/21, DOC-0013_RevB_User_Manual) and you noted, "*The set reference value(s) will determine the flagging of results in the report*". We acknowledge that you stated, "*A default reference value is provided for linear-based cardiothoracic index, as this is established in the literature. The clinician can choose to change the reference value as they wish depending on the practice of medicine. A default reference value is not provided for area-based cardiothoracic index because the reference has not currently been established by the practice of medicine*". However, you did not provide any reference to the literature from which this very specific CTR value of 0.569 for setting the threshold is identified. Per our understanding, there are different values available in the literature, suggesting that there may not be a complete agreement on what is the considered to be the upper threshold of normal CTR value. Please provide adequate justification for this CTR threshold of 0.569 with an appropriate reference such as any society guidelines, recommendations, widely accepted literature, as applicable. In the absence of this information, you may consider removing the default threshold and have the end user decide on how they want to use the continuous CTR index provided by the device. If you decide to remove this default threshold, please provide the corresponding updated software documentation. The automatic flagging of some cases based on this default threshold which is not well-established could impact patient management decisions and could lead to adverse effects for the patients. Please refer to Section III of the Technical Performance Assessment of Quantitative Imaging in Radiological Device Premarket Submissions guidance (https://www.fda.gov/media/123271/download).

7. You provided the schematic diagram for the device workflow in Section 5 (DOC-0008_System_and_Software_Architecture_Diagram.pdf) which includes a "Series Selector" and you noted, "*This item inputs one or more processed series and chooses the best one based on an ordered selection criteria. For example, DICOMs with thicker slices and contrast should be favored over those with thinner and noisier slices*". However, you did not provide any information on the actual "ordered selection criteria" in your submission. Please provide information on what "ordered selection criteria" are used in your device implementation, and how the functionalities for ensuring those criteria are implemented in your device. For example, how does the device identify which series have contrast or which series are noisier slice than others. Please also account for how these criteria will be applied automatically by the device during the clinical deployment of the device. This information is necessary for us to understand your device design and to evaluate that it is as safe and effective as the predicate device for its intended use. Please refer to Section VI-A of the Technical Performance Assessment of Quantitative Imaging in Radiological Device Premarket Submissions guidance (https://www.fda.gov/media/123271/download).

Software, Cybersecurity and Interoperability

8. You provided your software verification plan in DOC-0044 and software verification report in DOC-0045 which includes the verification activities "VER-012 Disabled internet access" and "VER-014 Reference value modification." We have the following comments about these activities and the associated test protocols:

a. For "VER-012 Disabled internet access," it is not clear if disabling internet access is a requirement of the software. If so, it is not clear how the software may function within the hospital network where it is likely to be installed on a device connected to the network for transfer of input DICOM data. Additionally, it is not clear how any vulnerabilities identified in the off-the-shelf software components used within the device would be addressed (software updates). Please clarify how this "disable internet access" functionality does not disrupt other interoperable devices and how the device performance would be impacted if the internet access could not be disabled.

b. The verification activity corresponding to "VER-014 Reference value modification" would be expected to test if the end user is able to modify the reference value. However, based on the test protocol, including the test steps and the acceptance criteria, "*When cardiothoracic index threshold and heart to chest are ratios are low (0.1 for both), test case should be flagged as positive for cardiomegaly and the reported metrics in the report will be displayed in a red color font*", this verification activity does not appear to be testing if the end user is able to modify the reference values but rather if the device flags the measurement when the value is above reference threshold. Please clarify this ambiguity and provide revised verification activity to demonstrate that the end user can modify the reference value (threshold).

Adequate software testing documentation is important to demonstrate with objective evidence that software development output meets its input requirement, and that the software conforms with user needs and intended uses of the device. Adequate software testing is also important because inadequately validated software could result in adverse health effects for the patient management. Furthermore, adequate verification and validation is important to demonstrate that your device is as safe and effective as the predicate. Therefore, as recommended in the "Software Testing as Part of Verification and Validation" section of FDA's guidance document "Content of Premarket Submissions for Device Software Functions" (https://www.fda.gov/media/153781/download), please provide verification in line with your device design to address the issues highlighted above.

9. You provided the list of unresolved anomalies in DOC-049_Unresolved_Software_Anomalies.pdf and noted that there is one unresolved anomaly. You also provided an impact of this unresolved anomaly as, "*Inputs are processed, but output files are not available in the outgoing folder*" and noted the risk as "Acceptable". You also provided a workaround for this anomaly as, "*Use run_docker.py for launching docker container*". However, it is not clear how the end user will know that the case was processed with no output written to the designated output folder and what action they need to take to retrieve the output. Therefore, as recommended in the "Unresolved Software Anomalies" section of FDA's guidance document "Content of Premarket Submissions for Device Software Functions" (https://www.fda.gov/media/153781/download), please provide evaluation of the impact of the anomaly on the device's safety and effectiveness, including operator usage and human factors considerations; and risk-based rationale for not correcting or fixing the anomaly in alignment with your risk management plan or procedure(s). Please also clarify how the end user would understand the impact of and workaround for this unresolved anomaly. It is important that appropriate measures have been taken to ensure anomalies will not affect safe and effective use of the device or result in adverse patient management.

10. You provided documentation on the cybersecurity controls (DOC-0056_Cybersecurity_Risk_Management_Report); however, you did not provide adequate information on

the authorization controls used to protect the device. Specifically, it is not clear if device implements layered authorization model with different privileges for different types of users (administrators, clinical users). Adequate authorization controls are important to comply with the requirements specified in section 524B(b)(2) of the Federal Food, Drug, and Cosmetic Act to provide a reasonable assurance that the device and related systems are cybersecure. It is also consistent with recommendations in Section 5 of the FDA guidance document "Content of Premarket Submissions for Management of Cybersecurity in Medical Devices" (https://www.fda.gov/media/86174/download) that cybersecurity functions, including authorization controls, be included in the device. Specifically, this guidance recommends that where appropriate, [manufacturers] employ a layered authorization model by differentiating privileges based on the user role (e.g., caregiver, system administrator) or device role. Therefore, please provide a description of how authorization is addressed in the design and define the privileges each role has on the device, including any differences in available connectivity. Additionally, please provide what authentication processes are associated with each authorization level.

11. Based on the information provided in your submission (DOC-0040 Software Description), your device meets the definition of a cyber device under Section 524B(c) of the Federal Food, Drug, and Cosmetic Act. However, you did not provide cybersecurity testing for the device. Adequate cybersecurity testing is important to comply with the requirements specified in section 524B(b)(2) of the Federal Food, Drug, and Cosmetic Act to provide a reasonable assurance that the device and related systems are cybersecure. Verification and validation testing of the cybersecurity controls is important to demonstrate that the controls have been implemented correctly and that they are effective during their intended uses. Security testing includes, but may not be limited to, requirement verification testing, static and dynamic code analysis, malformed input (fuzz) testing, vulnerability scanning, and penetration testing. FDA has recognized the consensus standards: AAMI/UL 2900-1:2017 and IEC 810001-5-1: 2021 which may be helpful to support cybersecurity documentation in submissions. These standards both include cybersecurity testing as a part of the device design and evaluation activities. See AAMI/UL 2900-1:2017, Clauses 13-19 or IEC 81001-5-1: 2021, Clauses 5.5-5.7 for cybersecurity testing types, like those listed above, that may support demonstrating that the cybersecurity controls and requirements are effective.

Therefore, please provide the security testing performed ensuring that it addresses the test types listed above, as appropriate, and ensure that the testing covers the end-to-end system, including but not limited to the DICOM Listener (including the Bonjour Protocol), implemented in your device.

- If testing was not performed, please perform security testing, and provide the associated test reports and your risk analysis for any findings.
- If testing was performed by a third-party, please provide the original report from the third-party, describe the scope of the engagement (i.e., how long, what they tested, whether it was open box or closed box testing, methods and tools used, etc.), and your assessment of the findings including any design documentation and additional testing if changes were made based on the findings.

The applicability of results from certain types of security testing (i.e., vulnerability scanning and penetration testing) degrade over time as new vulnerabilities and attack methods are discovered and may need to be reperformed if no longer relevant to current risks. Please define when the security testing types were performed and provide a justification for the applicability based on when they were performed.

12. Based on the information provided (DOC-056_Cybersecurity_Risk_Management_Report), it is not clear how the device detects, monitors, logs, and/or alerts users of security compromise. You provided some information on vulnerability management in Section 7 (DOC-0055); however, you did not provide any information on how the device logs security compromises and how the users are informed about them. Adequate detection, response, and recovery controls are important to comply with the requirements specified in section 524B(b)(2) of the Federal Food, Drug, and Cosmetic Act to provide a reasonable assurance that the device and related systems are cybersecure. It is also consistent with recommendations in Section 5 of the FDA guidance document "Content of Premarket Submissions for Management of Cybersecurity in Medical Devices" (https://www.fda.gov/media/86174/download), for manufacturers to address the following:

- Implement features that allow for security compromises to be detected, recognized, logged, timed, and acted upon during normal use.
- Develop and provide information to the end user concerning appropriate actions to take upon detection of a cybersecurity event.
- Implement device features that protect critical functionality, even when the device's cybersecurity has been compromised; and
- Provide methods for retention and recovery of device configuration by an authenticated privileged user.

Inadequate detection, response, and recovery methods can impact the safety and effectiveness of the device during a cybersecurity exploit. Therefore, for each item above, please provide a description of how the device design addresses each item, as applicable.

MINOR DEFICIENCY LIST

The Agency has identified minor deficiencies that can be resolved in a straightforward manner, but that need to be addressed to meet regulatory requirements or to prevent potential misbranding or adulteration.

Administrative Information

1. You provided the labeling information for the subject device in DOC-0013_RevB_User_Manual.pdf. While we acknowledge that most of the required information is included in your labeling, we have the following comments about the labeling:

a. You did not include any information on the design of your device including the underlying machine learning models and how they were trained. Please include this information in your User Manual to ensure that the end user has transparent information about the device design.

b. We acknowledge that you have included a summary of your performance testing in Section 7 of the user manual. However, this is very high-level information that does not allow the end user to understand how your device was validated. Please include complete details about the performance testing protocol including the details of test dataset, its characteristics, reference standard, performance testing results including the subgroup analysis, as applicable. Please note that the results may need to be aligned to your responses to performance testing related questions in this letter.

As required by 21 CFR 801.109(c), the labeling should include sufficient information so that the practitioners can use the device safely and for the purpose for which it is intended, including all purposes for which it is advertised or represented.

510(k) Summary

2. You provided a 510(k) Summary (DOC-0025_510k_Summary). We have the following comments about the 510(k) summary.

a. The 510(k) summary does not include **the indications for use statement**, as required by 21 CFR 807.92(a)(5). Please revise your 510(k) Summary to include this element. For additional detail on what to provide for this required element, please refer to Section G, and Appendices B and C of FDA's guidance document "The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]" (https://www.fda.gov/media/82395/download).

b. You are seeking clearance of a device that uses machine learning algorithm(s) as part of its key functionality. You have provided a high-level summary of performance data. However, this summary does not contain details on validation of the deep learning algorithm. To answer a demand for increased transparency around machine learning based device functions, and to fully satisfy the requirement in 21 CFR 807.92(b) that 510(k) Summaries provide "*an understanding of the basis for a determination of substantial equivalence*," we are requesting that you provide additional details on the validation of your machine learning derived outputs in your 510(k) summary. Specifically, please include (if you have not already):

i. Summary test statistics or other test results including acceptance criteria or other information supporting the appropriateness of the characterized performance
ii. The number of individual patients images were collected from
iii. The number of samples, if different from above, and the relationship between the two
iv. Demographic distribution including Gender, Age, Ethnicity
v. Information about clinical subgroups and confounders present in the dataset
vi. Information about equipment and protocols used to collect images
vii. Information about how the reference standard was derived from the dataset (i.e., the "truthing" process)
viii. Description of how independence of test data from training data was ensured

In addition to this information about your validation, we strongly recommend you provide some information about your training dataset in your device description.

FDA is offering a teleconference within 10 calendar days from the date on this letter to address any clarification questions you may have pertaining to the deficiencies. If you are interested in a teleconference, please provide (1) proposed dates and (2) a list of your clarification questions via email at least 48 hours before the teleconference to the lead reviewer assigned to your submission. We would like to emphasize that the purpose of the meeting is to address specific clarification questions. Please note that if the specific clarification questions are not received at least 48 hours before the teleconference, the review team might not be able to provide feedback. The teleconference is not intended for review of new information, test methods or data; these types of questions could be better addressed via a Submission Issue Q-Submission (Q-Sub). For additional information regarding Q-Subs, please refer to the Guidance for Industry and FDA Staff on Medical Devices: Requests for Feedback and Meetings for Medical Device Submissions at https://www.fda.gov/media/114034/download.

Least Burdensome (LB) Flag

The LB flag is an approach to allow submitters the opportunity for the informal review by or on behalf of Division management of an issue raised in an FDA request for additional information (i.e., a deficiency letter). The goal of the LB flag is to quickly address FDA requests that submitters do not believe are least burdensome or when submitters believe they are being held to a different standard than their legally marketed predicate device. The LB flag is not intended to clarify deficiencies, is not an appeal under 21 CFR 10.75, and is not intended to provide a review of a proposed response to deficiencies.

If you would like to throw the LB flag, FDA has several criteria that should be met before you submit your request:

- You should have tried to address your concern by discussing it with Division management before attempting to throw the LB flag. This discussion with Division management may take place as part of a teleconference (such as the voluntary teleconference held within 10 days following transmission of an Additional Information letter to clarify deficiencies), email, or a Q-Submission Submission Issue Request.
- Your flag should generally be limited to two topic areas. Topic areas are common premarket review deficiency categories that apply to many device types across multiple reviewing Divisions. Examples of topic areas include biocompatibility, sterility, reprocessing, software, electromagnetic compatibility, wireless, electrical safety, clinical, and non-clinical performance testing.
- If you would like to discuss issues pertaining to more than two topic areas, you should contact OPEQSubmissionSupport@fda.hhs.gov for more information.
- You should throw the LB flag within 60 calendar days of the date that FDA sent the deficiency letter.

Upon meeting the criteria, you should send a short email (e.g., 1-2 page) that includes: 1) a summary of the deficiencies under disagreement, 2) a summary of relevant communications with Division management, and 3) a proposed path forward. The LB flag should be sent to the lead reviewer and their Assistant Director. You should also copy OPEQSubmissionSupport@fda.hhs.gov on your LB flag email request. Within two business days of your email, your request will be acknowledged by the reviewing Division. If you do not meet the criteria for the LB flag, you will be notified in this acknowledgement email.

Your LB flag should contain sufficient information to determine whether the deficiency letter was not least burdensome, or you are being held to a different standard than your predicate device. FDA may request a phone call with you to discuss your concern further and intends to communicate feedback from Division management on LB flags through email no later than 21 calendar days of their receipt. Please note that the LB flag does not change the deadline for your response to the CDRH Portal. If you have any questions, please contact OPEQSubmissionSupport@fda.hhs.gov.