



July 11, 2024

Subtle Medical, Inc.  
% Jared Seehafer  
Regulatory Consultant  
Enzyme Corporation  
611 Gateway Blvd #120  
South San Francisco, California 94080

Re: K241329

Trade/Device Name: SubtleSYNTH (1.x)  
Regulation Number: 21 CFR 892.2050  
Regulation Name: Medical Image Management And Processing System  
Regulatory Class: Class II  
Product Code: QIH, LNH  
Dated: May 9, 2024  
Received: May 10, 2024

Dear Jared Seehafer:

We have reviewed your section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (the Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database available at <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm> identifies combination product submissions. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Additional information about changes that may require a new premarket notification are provided in the FDA guidance documents entitled "Deciding When to Submit a 510(k) for a Change to an Existing Device" (<https://www.fda.gov/media/99812/download>) and "Deciding When to Submit a 510(k) for a Software Change to an Existing Device" (<https://www.fda.gov/media/99785/download>).

Your device is also subject to, among other requirements, the Quality System (QS) regulation (21 CFR Part 820), which includes, but is not limited to, 21 CFR 820.30, Design controls; 21 CFR 820.90, Nonconforming product; and 21 CFR 820.100, Corrective and preventive action. Please note that regardless of whether a change requires premarket review, the QS regulation requires device manufacturers to review and approve changes to device design and production (21 CFR 820.30 and 21 CFR 820.70) and document changes and approvals in the device master record (21 CFR 820.181).

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR Part 803) for devices or postmarketing safety reporting (21 CFR Part 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 Part 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR Parts 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to <https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems>.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, 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](mailto:DICE@fda.hhs.gov)) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,



Daniel M. Krainak, Ph.D.  
Assistant Director  
DHT8C: Division of Radiological Imaging  
and Radiation Therapy Devices  
OHT8: Office of Radiological Health  
Office of Product Evaluation and Quality  
Center for Devices and Radiological Health

Enclosure

## Indications for Use

Submission Number (if known)

K241329

Device Name

SubtleSYNTH (1.x)

Indications for Use (Describe)

SubtleSYNTH is a software as a medical device consisting of a software machine learning algorithm that synthesizes a SynthSTIR contrast image of a case from T1-weighted and T2-weighted spine MR images.

Type of Use (Select one or both, as applicable)

Prescription Use (Part 21 CFR 801 Subpart D)

Over-The-Counter Use (21 CFR 801 Subpart C)

**CONTINUE ON A SEPARATE PAGE IF NEEDED.**

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## 510(k) Summary

**Table 1. Contact Details & Device Name**

<b>Date Summary Prepared:</b>	2024-07-09
<b><u>Contact Details</u></b>	
<b>Applicant Name:</b>	Subtle Medical, Inc.
<b>Applicant Address:</b>	883 Santa Cruz Ave, Suite 205 Menlo Park, CA 94025 United States
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<b>Correspondent Name:</b>	Enzyme Corporation
<b>Correspondent Address:</b>	611 Gateway Blvd, Ste 120 South San Francisco, CA 94080 United States
<b>Correspondent Contact:</b>	Mr. Jared Seehafer
<b>Correspondent Contact Telephone:</b>	(415) 638-9554
<b>Correspondent Contact Email:</b>	jared@enzyme.com
<b><u>Device Name</u></b>	
<b>Device Trade Name:</b>	SubtleSYNTH (1.x)
<b>Common Name:</b>	Medical image management and processing system
<b>Classification Name:</b>	Automated Radiological Image Processing Software
<b>Regulation Number:</b>	892.2050
<b>Product Code:</b>	QIH
<b>Additional Product Codes:</b>	LNH
<b>Device Class:</b>	Class II
<b>Legally Marketed Predicate Device:</b>	Predicate #: K201616 Predicate Trade Name: SyMRI Predicate Manufacturer: SyntheticMR AB

### ***Device Description Summary***

The SubtleSYNTH device is a software as a medical device consisting of a machine learning software algorithm that synthesizes a SynthSTIR contrast image of a case from T1-weighted and T2-weighted MR images. It is a post-processing software that does not directly interact with the MR scanner. Once a MR scan is acquired, a technologist sends the study from the scanner to a compatible medical device data system (MDDS) via the DICOM protocol. The compatible MDDS, then, makes the images available to SubtleSYNTH for processing.

SubtleSYNTH uses a convolutional neural network-based algorithm to synthesize an image with desired contrast weighting from other, previously obtained sequences such as T1- and T2-weighted images. The image processing can be performed on MRI images with predefined or specific acquisition protocol settings.

The SynthSTIR image is created by SubtleSYNTH and sent back to the picture archiving and communication system (PACS) or other DICOM node by the compatible MDDS for clinical review.

Because the software runs in the background, it has no user interface. It is intended to be used by radiologists in an imaging center, clinic, or hospital.

Note, depending on the functionality of the compatible MDDS, SubtleSYNTH can be used within the facility's network or remotely. The SubtleSYNTH device itself is not networked and therefore does not increase the cybersecurity risk of its users. Users are provided cybersecurity recommendations in labeling.

### ***Intended Use / Indications for Use***

SubtleSYNTH is a software as a medical device consisting of a software machine learning algorithm that synthesizes a SynthSTIR contrast image of a case from T1-weighted and T2-weighted spine MR images.

### ***Intended Use / Indications for Use Comparison***

SubtleSYNTH and SyMRI are both intended to generate contrasts from input data from MRI imaging systems. SubtleSYNTH generates only one contrast (SynthSTIR) while SyMRI generates multiple. SubtleSYNTH is indicated for spine, SyMRI is indicated for brain. Neither of these changes however reflect a different intended use.

### ***Technological Comparison***

SubtleSYNTH and its predicate device are both used for synthesizing contrasts. Though there are technological differences between the algorithm of SubtleSYNTH and that of

SyMRI, they do not raise different questions of safety or efficacy. SubtleSYNTH uses nonlinear filtering, i.e., convolutional neural network based filtering, for image enhancement. SyMRI utilizes a multi-delay, multi-echo acquisition (MDME). The data acquired is processed using a technique to generate multiple image contrasts simultaneously, such as T1, T2, PD and Inversion Recovery (IR) weighted images (including: T1-FLAIR, T2-FLAIR, STIR, Double IR and PSIR weighted images). SyMRI generates all the different image contrasts from the same acquisition, leading to enhanced image slice registration, owing to the absence of inter-acquisition patient movement.

### ***Non-Clinical and/or Clinical Tests Summary & Conclusions***

In addition to software verification & validation, performance bench testing was conducted to demonstrate safety and efficacy of applying SubtleSYNTH to generate SynthSTIR images using a convolutional neural network on clinically acquired STIR images.

To evaluate the performance of the software, Subtle quantitatively evaluated the 80 acquired studies recruited from clinical sites or hospitals. The acquired studies include Sag T1w, Sag T2w, and Sag STIR images from a wide range of sites, age range, manufacturers, scanner modes, and magnitude field strengths. Subjects ranged from 16 to 89 years old, and subject sex consisted of 40 females, 36 males, and 4 unknown sex. Due to data anonymization steps, ethnicity of the dataset is unknown. Studies were acquired on GE, Fonar, Philips, Siemens, and Toshiba MRI scanners; 42 series were with 1.5T scanners, 35 series were with 3T scanners, and one of each were acquired with 0.3T, 0.6T, and 1.0T scanners. There were 8 cord lesions, 20 degenerative diseases, 10 infections, 15 non-cord lesions, 17 trauma, and 10 normal series; these categories were assigned to collected images by an in-house radiologist. Data was sourced from populations in California, USA, and New York, USA. The data was used to assess the interchangeability of the SynthSTIR against the acquired STIR using Root Mean Square Error (RMSE), pairwise tissue contrast heatmap among the tissues, and a full Bland-Altman analysis to perform the analysis.

For each STIR (either from acquired STIR or SubtleSYNTH), multiple ROIs are drawn from five main tissues (Bone, Disc, CSF, Spinal Cord, and Fat). ROIs are randomly selected under each region. Specifically, 4 ROI were labeled with no overlaps. For each pair, only one case should be labeled where the ROI can be copied to the other image with relevant metrics on the case. The ROI is designed to estimate the intensity value for each tissue.

Two interchangeability studies were designed and performed to demonstrate interchangeability of SynthSTIR images against acquired STIR images by having

radiologists classify them into primary categories as well as secondary categories. The primary categories are (1) Degenerative, (2) Infection, (3) Trauma, (4) Cord Lesion, (5) Non-cord lesion, (6) Vascular, (7) Hemorrhage, and (8) Normal. In both studies, readers saw half SynthSTIR images and half acquired STIR images in the first session, had at least a one month washout period, and then saw the other half of both modalities in the second session.

In Study A, readers were presented with either a SynthSTIR or an acquired STIR only. In Study B, readers were presented with either a SynthSTIR or an acquired STIR and all other sequences that were acquired per the source's protocol (additional sequences and orientations were based on availability of the data, but had at least two different orientations). Study A and Study B had at least 4 readers each. Each study had the same 104 cases to review (12 cases per category with an even distribution in the subcategories, except for Trauma which had 20 cases). These cases were selected from 269 cases gathered to ensure that the cases had a variety of MRI scanners, field strengths, subject ages, and even distribution of sexes. Subject ages ranged from 1 to 89 years old, and subject sex consists of 51 females and 53 males. Due to data anonymization steps, ethnicity of the dataset is unknown. The cases were acquired on GE, Hitachi, Philips, Siemens, and Toshiba MRI scanners; 6 cases were with 0.3T scanners, 56 cases were with 1.5T scanners, and 42 cases were with 3T scanners. For Study B, all cases had at least non-synthetic Sag T1w, Sag T2w, and Sag STIR images, and had additional images based on availability such as non-synthetic Ax T1w, Ax T2w, Ax T2 FLAIR, Cor T1w, and Cor T2w. There were 12 cord lesions, 12 degenerative disease, 12 hemorrhage, 12 infection, 12 non-cord lesions, 12 normal, 12 vascular, and 20 trauma; these categories were assigned to collected images by an in-house radiologist. Data was sourced from populations in California, USA, and New York, USA. Note that although each clinical case was assigned a primary disease category, most cases have more than one condition, which could confound the results due to readers having different opinions on which condition is primary in an image. This was handled by providing readers recommendations on how to prioritize conditions when more than one is present, and asking readers to classify secondary categories in addition to the primary one.

Imaging data in the bench study and interchangeability studies was not used in the training of SubtleSYNTH. Subtle Medical maintains dataset repositories of training datasets and testing datasets to review and ensure that training data is not used for testing. The SubtleSYNTH training dataset consists of 424 cases of Sag T1w, Sag T2w, and Sag STIR images from a variety of MRI scanners, field strengths, subject ages, and even distribution of sexes. Subject ages ranged from 14 to 89 years old, and subject sex consisted of 193 females, 176 males, and 55 unknown sex. Due to data anonymization steps, ethnicity of the dataset is unknown. The cases were acquired on GE, Hitachi,

Philips, and Siemens scanners; 1 case was with 0.7T scanner, 6 cases were with 1.2T scanners, 2 cases were with 1T scanners, 254 cases were with 1.5T scanners, 1 case was with 2T scanner, and 160 cases were with 3T scanners. Data was sourced from populations throughout the USA.

Due to privacy practices, ethnicities of the training and testing data is unknown but can be inferred based on the population demographics from where they were sourced. The population demographics of data sources used for training and testing are as follows per the Census.gov July 2022 Estimates. In California, USA, the population of 39m people are distributed by race and hispanic origin as: White alone 70.7%, Black or African American alone 6.5%, American Indian and Alaskan Native alone 1.7%, Asian alone 16.3%, Native Hawaiian and Other Pacific Islander alone, percent 0.5%, Two or More Race 4.3%, Hispanic or Latino 40.3%, and White alone (not Hispanic or Latino) 34.7%. In New York, USA, the population of 20m people are distributed by race and hispanic origin as: White alone 68.6%, Black or African American alone 17.7%, American Indian and Alaskan Native alone 1%, Asian alone 9.6%, Native Hawaiian and Other Pacific Islander alone, percent 0.1%, Two or More Race 2.8%, Hispanic or Latino 19.7%, and White alone (not Hispanic or Latino) 54.2%. In the overall USA, the population of 333m people are distributed by race and hispanic origin as: White alone 75.5%, Black or African American alone 13.6%, American Indian and Alaskan Native alone 1.3%, Asian alone 6.3%, Native Hawaiian and Other Pacific Islander alone, percent 0.3%, Two or More Race 3%, Hispanic or Latino 19.1%, White alone (not Hispanic or Latino) 58.9%.

In the bench study, the Root Mean Square Error (RMSE) between the reference STIR and the SynthSTIR was determined to be 0.39 in normalized intensity units for all 80 cases. The heatmap of the contrast tissue ratio indicates that SynthSTIR maintained the consistent relative contrasts pattern with the STIR for MR scanned cases (which are from multiple sites, vendors, magnetic field strength, etc). Further, the cosine similarity matrix showed all elements above 0.9. For each tissue's Bland-Altman, the bias (the mean intensity difference between the SynthSTIR and acquired STIR) samples are randomly distributed near the zero lines without any increasing or decreasing trend for the difference when the normalized intensity value increases. Further, the 99% confidence interval analysis implies that there is no significant bias between the SynthSTIR and MR scanned STIR in terms of the normalized pixel value from the tissues (Bone, Disc, CSF, Spinal Cord, and Fat). These results prove that SynthSTIR is interchangeable with the acquired STIR in terms of the normalized pixel value from the main tissues (Bone, Disc, CSF, Spinal Cord, and Fat).

In the two interchangeability studies, the Primary Endpoint was that SynthSTIR images are interchangeable with acquired STIR images. Study A and Study B were successful if

the interchangeability between acquired STIR and SynthSTIR images is not significantly greater than 10%. Each study was evaluated overall and sub-analyses were performed within each Primary Category and scanner vendor groups.

As estimated by a Generalized Linear Mixed Model (GLMM), Study A demonstrated interchangeability of 2.12% (95% CI [-1.31%, 5.88%]). Using a bootstrap approach also resulted in the null being rejected with an interchangeability estimate of 2.17% (95% CI [-0.25%; 4.87%]). The strong alignment of the two methods in the point and 95% CI increases confidence in the conclusion that there is interchangeability between SynthSTIR and traditional STIR images.

As estimated by a GLMM, Study B had an interchangeability of 0.63% (95% CI [-4.19%, 5.9%]) and from a bootstrap 0.64% (95% CI [-3.34%; 4.50%]). Again, the confidence intervals from both the bootstrap procedure and taken directly from the GLMM model are in close agreement with each other.

Both studies met the primary endpoint, and it was concluded that SynthSTIR images are interchangeable with traditional acquired STIR images. In the sub-analyses, the primary endpoint was met for all Primary Categories and all scanner vendors in both Study A and Study B.

These results demonstrate that SubtleSYNTH is substantially equivalent to the predicate device.