Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Office of Device Evaluation

DATE: November 16, 2011

TO: File

CC: [redacted] (Consultant Reviewer, Toxicology)
Mitchell Shein (Branch Chief)

FROM: [redacted] (Lead Reviewer)

SUBJECT: P060039/S021/A001
Medtronic Model 4195 Attain StarFix™ Lead

OVERALL RECOMMENDATION

Based on my review of the submission text, discussions with supporting reviewers, as well as my review, **I recommend approval of the file**.

Signature	*Date*	*Signature*	*Date*
[redacted]		Mitchell Shein	
Biomedical Engineer		Branch Chief	
(Lead Reviewer)		(Management Oversight)	

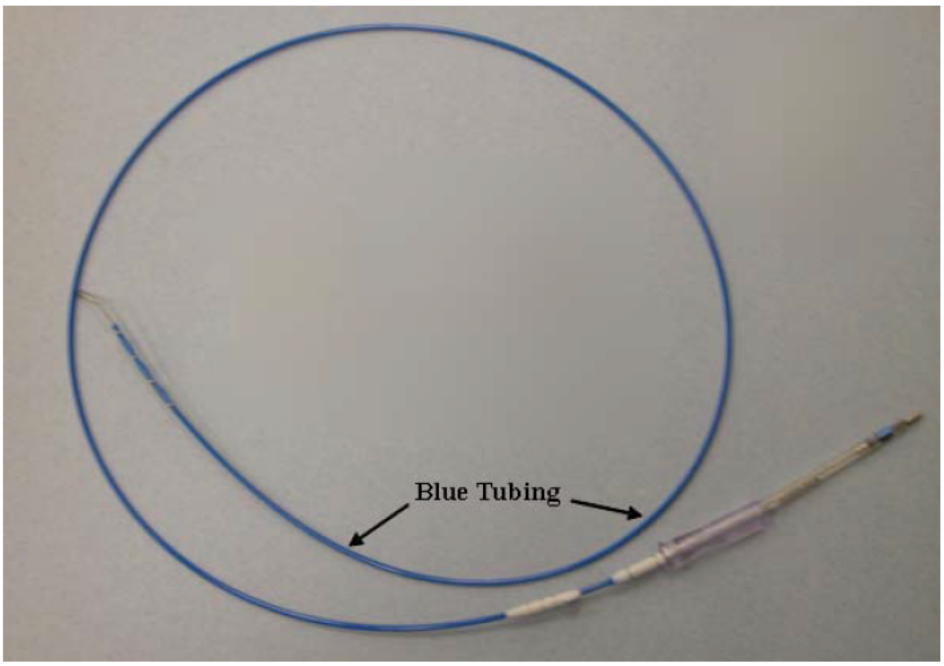
PURPOSE OF SUBMISSION

This supplement was submitted to request approval for a change in the requirement for the copper content in the blue polyurethane tubing utilized by the Medtronic Attain StarFix™ lead. The sponsor has received request from the tubing manufacturer to increase the maximum allowable copper concentration of the extruded tubing from [redacted] (b) (4) to accommodate for the variation in the manufacturing process. A major deficiency letter was sent to the firm after the first round of review and an amendment was submitted in response to that letter.

DEVICE DESCRIPTION

The Medtronic Attain StarFix™ Model 4195 steroid eluting, transvenous lead with deployable lobe fixation is intended for chronic pacing and sensing in the left ventricle via the cardiac vein, when used in conjunction with an implantable pulse generator or implantable cardiac defibrillator.

The combination product made up of a device (the Model 4195 lead) and a drug component (30 µg beclomethasone dipropionate/lead).



Description of Changes:

The lead contains blue [redacted] tubing in the push tubing component. The colorant used is [redacted] which contains copper. The colorant is blended into the tubing via a [redacted]

The current requirement for copper content in the push tubing component is a maximum of [redacted] ppm (parts per million). Medtronic has received a request from the tubing supplier to increase the allowable copper content to [redacted] ppm maximum. The change is intended to improve supplier yield.

Table 1: Proposed changes to the maximum copper specification for the Model 4195 lead

Model 4195 Lead Length	Current Copper Specification [parts per million (ppm)]	Proposed Copper Specification [parts per million (ppm)]
All Lengths	[redacted]	[redacted]

SOFTWARE VERIFICATION AND VALIDATION

There were no changes relevant to this issue. This section is not applicable to this submission.

LABELING

There were no changes relevant to this issue. This section is not applicable to this submission.

INDICATIONS FOR USE

There were no changes relevant to this issue. This section is not applicable to this submission.

TOXICOLOGICAL RISK ASSESSMENT

On review of the original submission, there was concern that no data were provided, or assumption made, about the rate at which the compound is released from the device. Also, the risk assessment was focused on the toxicity of the inorganic copper component of the molecule but would have been more appropriate to address the risk posed by the copper phthalocyanine (CuP) compound molecule. Toxicity profiles were provided for (b) (4) because both had the potential to be leached from the tubing.

A new toxicological risk assessment was provided by the firm and reviewed by [redacted] (Toxicologist, OSEL/DB). This assessment provided a Tolerable Intake (TI) value for copper phthalocyanine and compares this value to the dose of the compound released from the device. The TI value for (b) (4) is based on a NOAEL of 100mg/kg/day. It is possible to derive a parenteral TI from the oral toxicity NOAEL reported in the study conducted by the Japanese MLHW. The OECD used this value as the basis for their Estimated Dose of Low Concern (EDLC) value of 0.2 mg/kg/day for oral exposure to this compound. Application of a default conversion factor of 10 for route-to-route extrapolation to derive a provisional parenteral TI value yields a value of 0.02 mg/kg/day, which is identical to Medtronic's "internal health criteria" of 0.025 mg/kg/day.

Medtronic has estimated that (b) (4) mg of copper phthalocyanine are contained in 2 leads. One might conservatively assume that all of the dye would be released over 1 year. Under this exposure scenario, the average daily dose of the dye received by a 70 kg patient would be:

(b) (4)

This value is well below the TI value proposed by the submitter and well below the TI derived from the OECD EDLC. As a result, it appears that there is little likelihood of adverse noncancer effects occurring following patient exposure to the amount of copper phthalocyanine present in 2 leads. The sponsor has addressed this deficiency and there are no remaining toxicological risk concerns.

BIOCOMPATIBILITY

The sponsor included a toxicity profile that discussed Irritation and Sensitization. Skin reactions did not occur with adult volunteers using a patch test with (b) (4) blue in petrolatum, nor did irritation occur in a 24-hour covered patch test using phthalocyanine blue on abraded or intact rabbit skin. (b) (4) blue was also reported to be non-sensitizing in rats and mice according to a research paper cited by the sponsor. There are no additional biocompatibility concerns for this issue. There was initial concern that the biocompatibility was not adequately addressed, however, the toxicological risk assessment and toxicity profile in the amendment were sufficient to address toxicology and biocompatibility concerns.