C Laser Inc.

April 28, 2018

Division of Dockets Management,
Food and Drug Administration, Department of Health and Human Services, rm.1-23,
5630 Fishers Lane, rm. 1061,
Rockville, MD 20852

Re: Petition for Administrative Reconsideration under §10.33.

Please see attached, our petition for Administrative Reconsideration under §10.33 of the company's de novo request DEN 170050 that was denied on April 3, 2019.

Per advice rendered by phone by the division of dockets management, this petition has been electronically filed. Please advise if a paper copy would be needed in addition to the one filed electronically.

I can be readily reached at my cell: 765-891-0721 or through my e-mail: srinidoc@hotmail.com .

Sincerely,

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LILA
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Petition for Administrative Reconsideration of DEN 170050 under §10.33. Severe and serious procedural errors identified in the denial of de novo DEN 170050.

A. Decision Involved

This is a petition under §10.33 for an Administrative Reconsideration of the de novo request, DEN 170050 for the medical device Srilas 7 Low Intensity Laser Ablation System (or Srilas 7), a percutaneous, needle based selective ablation device. The removal of Srilas 7 from automatic Class III to be placed in Class II or I was denied. The denial order, a significant FDA decision was dated April 3, 2019. This petition has been electronically filed within 30 days after the denial decision and must therefore be considered as being filed timely.

B. Action(s) Requested

1. Overrule the denial order and remove Srilas 7 from automatic Class III to be placed in Class II (or I), since
    a. Srilas 7 is the lowest power medical laser and substantially safer than similar but approved percutaneous, needle based energy emitting ablation devices and;
    b. The denial order while ignoring the least burdensome approach was based on a seriously erroneous review process.
2. Recognize Srilas 7 as a "non significant risk" (NSR) device for the purpose of a clinical study or otherwise, since Srilas 7 is safer than NSR device examples per FDA's own guidance document under UCM126418.
3. Recognize Srilas 7 as a breakthrough device in patient's best interest, consistent with FDA's own written communication dated October 28, 2010 granting the device expedited review status.

C. Statement of Grounds

Definitions: 'Company' means C Laser Inc. or the sponsor of the de novo and the submitter of this petition. 'Division' means FDA's Division of Neurological and Physical Medicine Devices, Office of Device Evaluation, where the DEN 170050 was reviewed and denied. 'Submission' means the company's current de novo submission DEN 170050 that was denied. Consistent with §10.33 petition requirements, NO new material has been added other than what is already present in the written communications and company's FDA filings. Consequently, this petition and the statement of grounds are based on strong written evidence.

Materials prevented from public disclosure under §10.20 (j)(2): Certain parts or all of this petition may be subject to §10.20 (j)(2) and prevented from public disclosure. These include items described under §10.20 (j)(2) a-f, but may also include representative diagrams, tables and figures used in the submission which are reproduced here to support this petition. The company has presented them as separate references to which this petition is referring and has marked them as possible §10.20 (j)(2) materials. Srilas 7 has been successfully used to treat intractable pain in law enforcement officials who have been injured in the line of duty, providing them with both immediate and long term pain relief, and without any adverse effects or side effects whatsoever. In addition to reversing the disability from pain in these individuals, the device treatment results in functional improvement not seen with other drugs or devices. Opioid medications and medication management are no longer required in those individuals due to the quality of pain relief obtained. Accordingly, the company

believes that the device could carry major significance to the US armed forces in the treatment of chronic intractable pain in soldiers injured in the line of duty. For these reasons, the commissioner can at his discretion, determine which parts of this petition can or cannot be disclosed publicly.

Petition is in the public interest and in the interest of justice: This petition is in the public interest, patient's best interest and in the interest of justice. Moreover, this petition and the supporting evidence it presents demonstrate the following:

(1) Relevant information or views contained in the administrative record (i.e. the submission DEN 170050 and other filings related to the device Srilas 7) were not previously or not adequately considered.
(2) The petitioner, C Laser's position is not frivolous and is being pursued in good faith since evidence supporting this petition is found as written documentation.
(3) The petitioner, C Laser has demonstrated sound public policy grounds supporting reconsideration since the actions sought by the company in this petition are relied upon published FDA guidance documents.
(4) Reconsideration is not outweighed by public health or other public interests and in fact is in the patient's best interest.

Background: The aforementioned DEN 170050 was filed in September 2017 (confirmed received by the FDA on 9/19/17). DEN 170050 represents an innovative, safe and effective medical device technology called "Srilas 7 Low Intensity Laser Ablation System (LILA®)" further referred to as Srilas 7. Srilas 7 selectively eliminates only the unmyelinated axons at its site of action without any effects on myelinated axons and non neural tissue. Under this innovation, *chronic pain transmitted* by unmyelinated axons can be selectively reduced or eliminated without causing any adverse effects or side effects since the device has no action on myelinated axons and non neural tissues. See Table A below (as discussed in the submission p93, p381, p391):

Somatic Myelinated Axons	Somatic Unmyelinated Axons (C fibers)
Motor functions Sensory functions Pressure Acute pain transmission	 Light pressure Chronic pain transmission
Diameter: 2 microns and above	Diameter: 0.3-1.5 microns

Until the invention of Srilas 7, unmyelinated axons could not be selectively eliminated. All drugs and ablation devices in use today perform a non selective function i.e., they affect all axons both myelinated and unmyelinated as well as affect 'non neural' tissues. Hence, the nonselective drugs and devices almost always have side effects or adverse effects, since besides affecting axonal transmission from unmyelinated axons, they also affect myelinated axons. Myelinated axons are responsible for higher functions such as sensation and motor activities. Removal or affliction of myelinated axons may result in motor weakness and or loss of sensation, a common side effect of radiofrequency or RF ablation while RF ablation is considered 'the gold standard' of ablation. RF ablation is commonly used for treating pain at the spinal facets in patients who fail to improve with conservative treatments. While RF ablation is a whole tissue ablation device, meaning, the energy emitted at the tip of its needle probe destroys all tissues on contact, Srilas 7 is not a whole tissue ablation device, since the energy emitted at its needle tip

eliminates only the unmyelinated axons. In other words, Srilas 7 affects only part of a tissue, in this case one part of a neuron namely the unmyelinated axons, axons being only one part of the tissue, one part of the cell or the neuron. In comparison with existing FDA approved devices, Srilas 7 is substantially safer.

Both humans and dogs treated with Srilas 7 experienced immediate and long term pain relief along with spectacular improvement in function in the absence of any side effects or adverse effects whatsoever. The company wants to point out that it is not using the terms "spectacular improvement in function" lightly and that the functional improvement seen in both humans and dogs have not been described or demonstrated previously with approved drugs or devices in the treatment of focal pain symptoms. These effects have been captured on video, documented and witnessed by independent monitors and comprehensive information obtained thereof has been submitted to the FDA in the company's filings. Although clinical data demonstrates significant effectiveness in patients experiencing focal pain symptoms who have failed approved treatments, the DEN 170050 does not include a clinical indication in its IU and IFU statements for the treatment and diagnosis of any disease. Pain is a symptom of a number of disease conditions. The device's IFU appears a tool for ablation like other 510k ablation devices without a clinical indication to treat or diagnose a disease. It does however include FDA's language as reflected in its October 28, 2010 communication wherein FDA declared in writing that the device is granted expedited review status and noting that the device would be in the patient's best interest when *"no approved alternative exists for patients with uncontrolled pain using currently available treatment, or for patients who are contraindicated for pain medication."*

Srilas 7 is a breakthrough device which has been awarded multiple US and international patents for its underlying technology. Specifically, as mentioned above, this is the first time a device is demonstrating the selective elimination of unmyelinated axons and in doing so is devoid of any adverse effects and side effects, thus exhibiting superiority over other ablation devices and drugs that do not offer selectivity and hence prone to adverse effects and side effects. Srilas 7 is a US invention, tested exclusively in US institutions and laboratories and as mentioned earlier, it has been used in dogs and humans again only in the US.

FDA Interactions: Severe and serious procedural errors in the device review process leading to the de novo denial order, the basis for this petition. These severe and serious procedural errors supported by written evidence are further elucidated as follows:

1. **Off-centered, nonspecific, over generalized review methodology by the division that lacks scientific rationale and logical reasoning, a severe and serious procedural error.** The submission for Srilas 7 lacks ambiguity and is straight forward as outlined below:
    a. Srilas 7 is another needle based ablation device comparable to RF ablation devices (e.g. NT1000). Its needle probe placement is identical to that of other approved needle probe based energy emitting devices such as RF and laser devices.
    b. Physicians who already know how to use RF needle based devices, use the same approach to place the Srilas 7 at the same anatomical targets (e.g., spinal facets). See Reference Figure 1.

    A detailed discussion appears in the submission on p264-276 on how physician (Anesthesiologists) place various needles including acupuncture needles at their respective anatomical targets without any problems and how millions of such procedures are being performed in the US on a regular basis without any safety concerns. The submission specifically reiterated multiple times that Srilas 7 does not entail a new procedure method for placing its needle probe and such placement is a procedure that is

the same or similar to all other needle based procedures. This key fact has been continuously and regularly ignored by the division resulting in safety concerns and deficiencies that would not have risen if this key fact has been considered and not omitted in the first place. The company notes this is to be a serious fact omission by the division, consequently leading to serious and severe errors in the division's review methodology and review process.

c. The difference between Srilas 7 and other needle based energy emitting devices is what is being emitted at the tip of the needle probe. **This distinction is critical and extremely important since all things remaining the same, the energy emitted at the Srilas needle tip is substantially less than other approved energy emitting needle probe devices and even less than that of a commercial laser pointer!** See Reference Table 1.

   As can be seen in the referenced table, Srilas 7 is less powerful than that of a commercial laser pointer, while being tens of thousands of times less powerful than approved laser and RF devices. It follows that Srilas 7 is much safer than other approved devices, since all other elements other than energy emission are essentially similar or same. A comprehensive discussion of Srilas 7 with approved needle probe based energy emitting devices is found in the well-organized submission under the heading: "Device Comparison with approved 510k devices" on p102-p116 of the submission, which is also bookmarked in its electronic copy. A number of tables and figures appear in this section following FDA's own published guidelines that lay the fundamental foundations of safety and effectiveness of Srilas 7 in comparison with other 510k devices and concluding that Srilas 7 should be removed from automatic class III following those well established guidelines. In fact, tests conducted at higher institutions show that Srilas 7's laser emission is protective and safer than just a needle placement, as it reduces the pain sensitivity from those needle placements by more than 58%. Hence, Srilas 7 is more safe than acupuncture needle placements on spine (see p105, p178 of the submission).

d. Effectiveness of laser emission at Srilas 7's needle tip. The question should then arise for any scientist, physician or a reviewer that whether the device is capable of ablation at all at such low energy levels i.e. whether the device is effective in saying what it can do, since the safety question has already been addressed as above. To address the effectiveness question, the company performed not just one but 4 different animal studies at higher institutions of learning and each of those institutions concluded independently of the other, that Srilas 7, while unable to perform whole tissue ablation, is able to selectively eliminate only the unmyelinated axons, leaving myelinated axons and non neural tissues intact. Therefore, tissue preservation which is typically absent in approved needle based RF and laser devices, is present in Srilas 7. The changes from Srilas 7 could be demonstrated at the electron microscopy level wherein unmyelinated axons were eliminated in the test samples as opposed to controls and also through behavioral tests that correspond and relate to function of unmyelinated axons. In addition, humans and dogs with focal pain and related disability treated with Srilas 7 experienced both pain relief and resolution of the *focal pain related disability* immediately after the treatment and kept those improvements for several months to years indicating an ablative effect on the unmyelinated axons rather than some temporary effect.

In light of the above facts, it is evident that the division conducted an off-centered, overgeneralized review that lacks scientific rationale and logical reasoning through a series of fact omissions which can be readily seen in the division's written communications and feedback.

In other instances, as shall be further discussed, the division's written communications indicate that the current and previous deficiencies were generated by altering the company's facts of the submission and submission data. These instances supported by written evidence indicate that major deficiencies could not have been formulated by the division, if the omitted facts were considered and facts of the submission were not altered. In other words, severe and serious procedural errors were undertaken by the division resulting in the denial of the de novo, leading to this petition directly to the commissioner.

2. **The division deferred and dodged a proper risk based assessment of the device Srilas 7, the fundamental aspect and primary function of any review of a de novo submission.** The company wants to emphatically state, that the division did not perform a proper risk based assessment of the technological characteristics that is specific to Srilas 7, the device under submission.
    a. In 2012, the Srilas 7 was submitted initially as a 510k device comparing its technological characteristics to other needle/probe based laser and RF devices (see submission p32). In response, the division noted, "*The VersaPulse cleared under K011703 and Diomed 15/30 cleared under K051996 are lasers that have an output on the order of Watts (W). However, your device outputs only milli-Watts (mW). We believe your predicate devices are not appropriate. Please select a predicate device that has similar technology (low level laser).*" Following suit however, the company was unable to find a suitable predicate **since the power emissions of Srilas 7 was substantially lower than lower power lasers and hence had to be filed as a de novo device.** See Reference Figure 2 (see submission p114):

    Srilas 7 has the lowest power emissions of all invasive laser tissue ablation devices. Additionally, approved 510k tissue ablation lasers do not have a number of safety controls and safety features present in Srilas 7. It should be noted that the de novo confers an automatic class III to any device submitted as a de novo which is a safety precaution that applies to all novel devices even if they pose no harm and their safety profile is the same as another 510k device. Rarely, the de novo devices in this class may truly belong to a Class III following the PMA pathway. In the case of Srilas, it was readily evident, that its power emissions were so low and substantially lower than low level lasers that the device was having no effect on whole tissues unlike other needle based ablation devices. It was then imperative on part of the division to first recognize the device as being substantially safer than other 510k devices. **This logical and fundamental safety conclusion was deferred and dodged by the division while making deficiency statements on other concerns. The division failed to recognize that unmyelinated axons perform no higher functions and their elimination does not result in adverse effects or side effects.**
    b. Besides dodging the fundamental safety conclusion that should have been naturally arrived at, the division undertook classify and convert Srilas 7 into a significant risk device, without any scientific justification, and for the only reason it was in a de novo submission as an automatic Class III. The division made several statements that were speculative, nonfactual and applied to other laser devices and ablation devices in general but not to Srilas 7 (see submission's cover letter p5-18 for a detailed discussion). In its 2013 deficiency letter dated 4/18/13, the division noted that the device study would be a significant risk, noting there could be collateral damage during its use on spine. These statements were not substantiated by FDA's own guidance documents which state low

level lasers in the treatment of pain are "non significant risk devices." Furthermore, collateral damage means other tissues other than unmyelinated axons are being affected which would mean that the device performs same like other 510k devices and should not have been placed in de novo in the first place. Additionally, in the same FDA guidance document, there appears "non significant' risk use of a device on the spine wherein, the device is placed directly on the spinal cord after breaching the spinal canal. The company pointed out, that Srilas 7's needle probe placement is no different than RF needle placement on the spine while RF emits 1 million times more energy than Srilas 7 at its needle tip and still it does not breach the spinal canal. Accordingly, Srilas 7, which is incapable of tissue destroying energy does not breach the spinal canal. Therefore, on a head to head comparison of other 510k devices whose clinical use is similar and the same as Srilas 7, the latter with its substantially reduced energies would also be substantially safer. See Table 2b below. (see submission p30-31).

Division's Unsubstantiated Statements	**Actual Facts**
Srilas 7 needle is placed in the neuroforamen	No, Srilas 7 needle is never placed in the neuroforamen. It is placed at the spinal facets which is a bony structure outside of the spinal canal, impenetrable to needles. Integrity of the spinal canal and spinal neuroforamen are never affected at any time.
Srilas 7 needle is repetitively used	No, Srilas 7 is placed one time at the spinal facet for just 5 seconds which provides long term pain relief without requiring repetition. This is far less than the 5-20 minutes required for acupuncture needle placements at the spinal facets (DU and BL points) while such placements are repeated multiple times. Spinal procedures with approved needles take at least 20 min to 1 hour to perform.
Srilas 7 could potentially cause neuropathic pain	No, Srilas 7 reduces unmyelinated axons while neuropathic pain is the result of increased unmyelinated axons, a completely opposite process.

A device's spinal placement alone does not qualify the device study to become a significant risk without the elucidation of what those risks may be. FDA's own guidance document describing how a device placement on spine on exposed spinal cord would still be a non significant risk (NSR) study. The following is a comparison to guidance described in FDA's document UCM126418 on page 6, regarding placement of devices on spine:

> "An investigational study of a sensor pad to find out if the device can detect the electrical activity of the spinal cord may be NSR, if the study of the sensor pad takes place at the same time as the planned surgical repair of the spinal cord, if all the following are true (see Table 2ba below. See p31-33 of submission):

Sensor Pad Placement (FDA Criteria)	Srilas 7 placement (Factual)
Placed on spinal cord directly (after spinal canal has been breached)	Placed on spinal facets which is a bony structure outside of the spinal canal and impenetrable to needles. Spinal canal and spinal neuroforamen are intact and always remain intact
Repair of the spinal cord would occur anyway	Not applicable, as the integrity of the spinal canal and spinal neuroforamen is never breached
The sensor pad does not present a potential for serious risk to the health, safety, or welfare of a subject (for example, placing the pad would not prolong or interfere with the operation)	Placement time on spinal facets is 5 seconds which is far less time than that required for Acupuncture procedures and for other needle based spinal procedures. Hence, there is no potential for risk to the health, safety, or welfare of a subject. Srilas 7 is much safer than other spinal procedures. There is absolutely no potential for serious risk since the integrity of the spinal canal and spinal neuroforamen is not breached
The sensor pad is not implanted	Not applicable as nothing is implanted
The pad is not of substantial importance in diagnosing, curing, mitigating or treating disease.	The device is <u>not</u> of substantial importance in diagnosing, curing, mitigating or treating disease in this case as it is not directly placed on the spinal cord and has no effects on the spinal cord like the sensor pad placement does. In fact, pathology of the spinal cord and that of the neuroforamen and spinal canal cannot be addressed by Srilas 7.

The logical reasoning derived from the above information as found in FDA's own guidance document should conclude Srilas 7 to be an NSR device, safer than FDA's own example of device use on spine or otherwise. Unfortunately, there is no evidence at all, from any of division's activities and communications that logical conclusions were arrived through application of FDA's own guidance documents. A proper risk based assessment of the device, a fundamental and primary function of any de novo review process was therefore never performed.

c. Misleading and deceptive communications regarding risk based assessment. As mentioned above, the company's submission of DEN 170050 was confirmed received by FDA on September 19, 2017. No response was received from the division within the 120 days mandated by law for a response to a de novo submission. The company then filed a *Missed MDUFA Decision Communication* asking for a response. The division then responded on March 26, 2018 after 6 months or 180 days with a 16 page additional information (AI) or the deficiency letter. **This letter did not include a risk based assessment of the device**. The company replied with a comprehensive response to the deficiencies (confirmed received by FDA on 6/4/18). In that response, the company pointed out as above that the division has deferred and dodged a risk based assessment which is a fundamental and primary function of any de novo review process. In response, the division noted the following in its e-mail communication of 6/12/2018 (see copy of this communication in :

"Also, to address your first statement, "Absent or deferred risk based evaluation by the FDA required to remove Srilas 7 from automatic class III designation and to be placed in Class II, the primary goal of any de novo review.": Please note that the DeNovo program is intended for review of Class I and Class II device systems only. By accepting the Srilas 7 for DeNovo review and by not issuing any deficiencies regarding high risk levels in our Additional Information letter, ***we are giving a de facto acknowledgement that the FDA does not consider the device to be a high risk at this time.****"*

The above statement then lead the company to believe that the device has been removed from Class III. The additional correspondences and filings from the company confirm the company's understanding that the device was removed from automatic Class III and pending placement in Class II. The company not only thanked the division for its acknowledgement, but also filed subsequent responses including the aforementioned e-mail noting the "de facto acknowledgement" by the division that explicitly indicated that the device, no longer being considered a Class III, had been removed from Class III. **Never did the division once, object, deny the company's inference. It was also the company's inference that the submission was set to a path to clearance since the device was no longer considered an automatic Class III. The communications from the division which is explicitly stated above is quite contrary to the de novo denial statement (de novo denial dated April 3, 2019) which appears as follows:**

"Based upon the information within your De Novo request, FDA concludes that you have not demonstrated that this device meets the criteria under section 513(a)(1) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 360c(a)(1) (the FD&C Act) for classification into class I or II. This decision is based on the fact that you have not provided sufficient information to demonstrate that the probable benefits of the device outweigh its probable risks to health. Additionally, you have not provided sufficient information to enable FDA to develop special controls to mitigate probable risks to health and provide reasonable assurance of safety and effectiveness.
This order, therefore, declines your request and the device remains in class III (Premarket Approval)."

These instances indicate that the division not only did not perform a proper risk based assessment that is required of any de novo submission, but used the de novo definition improperly to perpetuate the company's device in automatic Class III and although, there was no evidence whatsoever that the device was less safe than similar 510k devices. Additionally, when the company raised questions about its risk assessment not being found in its deficiencies under the current de novo DEN 170050, the division used deceptive communications assuring the company that it provides a "de facto acknowledgement" and that the device was not considered a Class III. Finally, the division admits in writing that it *did <u>not</u> issue* any high risk level deficiencies (since there weren't any), indicating that the device met the safety requirements of Class II or Class I. These facts alone should suffice the commissioner to grant the petition under §10.33 and to reverse the division's denial order. Srilas 7 should therefore be removed from automatic Class III and afforded clearance.

3. **Contrary to the statement found in the de novo denial letter which imply that special controls are either inadequate or absent, both general and special controls are present in Srilas 7 and exceeded those that are required for similar, but approved laser devices** (See attached special controls)**.**

   The division, in its communications, not once raised any deficiency questions regarding any of the special controls which strongly indicate that the device's special controls far exceeded the safety of approved 510k laser devices. These facts along with the evidence presented as above indicate the division employed serious and severe procedural errors in arriving at its denial order.
4. The de novo denial lists under "histology" that the division's request for cross sections over longitudinal were not met by the company. **This petition shall demonstrate with written evidence that the division's request for cross sections lack scientific rationale and logical reasoning.**
   a. Lack of substantive arguments from the division on the histology evidence provided. The division has consistently failed to make a substantive argument on the information provided in the initial submission as well as to the responses to the deficiencies provided by the company. The de novo denial mentions deficiency #5 which when perused shows that the division does not make a logical argument for more information over the evidence already provided. Laser mediated ablation which is cellular and sub-cellular is based upon the cellular structures absorbing the laser energy, while the absorbed energy quickly disrupts the specific cell absorbing that energy, in this case the unmyelinated axons. This type of laser mediated ablation which is also known as biophotonic ablation or plasma mediated ablation is quite rapid, happening in a matter of seconds or less than a second, whereby cell contours vanish without a trace (see submission's EM study p128-168). Laser mediated cell ablation is cell specific, in this case specific to unmyelinated axons, wherein the unmyelinated axons are selectively eliminated by the laser emission from Srilas 7 through laser energy self-absorption and self-destruction. The cell contours vanish without necrotic remnants under this process. Hence, there are no necrotic remnants available as opposed to regular whole tissue ablation where such necrotic remnants can be readily observed. The division formulates the deficiency #5 under a serious misinterpretation of facts considering the laser mediated elimination of unmyelinated axons as being the same as whole tissue ablation where necrotic remnants would be seen and generalizing that both whole tissue ablation and ablation by Srilas 7 are the same. The actual language of the division's deficiency #5 which is missing in the de novo denial is reproduced below for clarity:

      "Immediately after treatment, it is expected that necrotic residue would be found in the place of the ablated axon, rather than the healthy tissue with reduced axons seen in the images."

      The division acknowledges that "healthy tissue with reduced axons" are seen in the images indicating the disappearance of (unmyelinated) axons without necrotic tissue, a fact that is consistent with laser mediated ablation. However, why necrotic residue, a property of whole tissue ablation should be expected to be seen in laser mediated cellular ablation is beyond anyone's understanding. The division's statement which on one hand acknowledges the device's ability to eliminate axons (unmyelinated) while conserving healthy tissues (myelinated axons, non neural tissues), lacks logical reasoning and

scientific rationale when asking for information that is generally found in devices that perform whole tissue ablation.

b. The need for cross sections emphasized by the division as providing "a more direct comparison" and "complete picture of ablation" are debunked by the company's comprehensive responses which have repeatedly shown the lack of scientific rationale or logical reasoning in the division's request for cross sections. For e.g. cross sections neither provide a better comparison nor do they provide a complete picture of ablation. In fact, the division, while making no substantive arguments on the information already provided by the company, undertook to discredit the submission's histology studies by focusing on an unrelated published study based on Capsaicin induced chronic degeneration of unmyelinated axons (Cheepudomwit et al. 2008). The division introduced this new but unrelated information retrospectively leading to the company's filing of meeting minutes disagreement. Chronic degeneration has no relationship with ablation and the related images provide no information on ablation let alone providing a complete picture (see meeting minutes disagreement Q140104/S001/A003 filed by the company, p8-10). See Table (4b) below:

Characteristics	**C Laser's EM Study**	**Cheepudomwit et al.**
Laser Ablation	Yes	No
Ablation effects at different power settings	Yes	No
Elimination of Unmyelinated Axons	Yes	No, degeneration present, nothing is eliminated
Myelinated axons shown with full contours	Yes	No
Non neural elements within sciatic nerve shown?	Yes, micro blood vessels and red blood cells seen	No
Total number of high resolution EM images	21	0, only 2 low resolution images present, 4 non EM poor resolution images present
Mechanism of Action relevance to laser	Unmyelinated axons eliminated through laser absorption	Not relevant to laser. Unmyelinated axons remain in a degenerated state through capsaicin induced, macrophage invasion of the unmyelinated axons

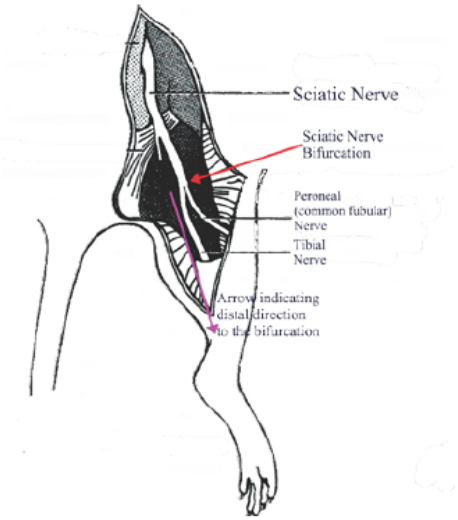
Basis of a medical device present	Yes	No. Capsaicin application on open skin triggers a very painful response. There is no place in clinical medical science for capsaicin to be applied directly to an exposed nerve
Study methodology includes damage to integrity of the sciatic nerve as a whole	No	Yes. The sciatic nerve is transected and sutured to nearby muscles. It is unclear whether this damage itself would be responsible for any stated degeneration changes suggested by the article

The above comparison readily shows that the division has not made a case either through example or otherwise, that new information would be needed in the form of cross sections to understand the effects of Srilas 7 and that the de novo denial is based on lack of substantive arguments on information already provided by the company and is a result of serious omission of critical information which when considered would have cleared Srilas 7. These instances further support the company's contention that the division's de novo denial had severe and serious procedural errors and should be overturned.

c. The division included "add-on" materials to the meeting minutes of the August 6, 2018 meeting that were never discussed in the first place. These "add-on" materials were so absurd that no scientist including the FDA scientist present at the meeting could have possibly made those suggestions. More specifically, these include the following:

    i. A conversation, as if the FDA scientist brought in by the division explicitly suggested making a reference point at the sciatic nerve bifurcation to examine the effects of the ablation with a cross section at 1 cm distal to that reference point. The suggestion has no scientific rationale since there is no sciatic nerve at 1 cm distal to the bifurcation where the sciatic nerve branches off into two separate nerves. This absurd add-on material included by the division when left undisputed would suggest that the company didn't have a counter argument. The company's meeting minutes disagreement demonstrates how the division's suggestions have no scientific rationale or logical reasoning as follows. See fig. (4c) below (See company's meeting minutes agreement Q140104/S001/A003, p5-7)

Rat Sciatic Nerve: At the bifurcation, the sciatic nerve ends, branching into tibial and peroneal nerves. Distal to the bifurcation, there is no sciatic nerve



ii. A conversation, as if the FDA scientist brought in by the division presented the aforementioned literature (Cheepudomwit et al. 2008) "to show figure 3 to explain how selective unmyelinated axon injury could look like after ablation." Not only was there no ablative injury, but the so called figure 3 was actually a longitudinal section and not a cross section which is what the division purports to show as an example of a cross section. The FDA scientist present at the meeting made no such suggestion, since it would be self-denigrating, so as to show chronic degeneration as an example of ablation and a longitudinal section as an example of a cross section thereby indicating that he had no ability to distinguish between degeneration and ablation as well as longitudinal vs. cross sections.

How could any company respond to materials that were not discussed at all? The above instances provide unequivocal written evidence wherein the division attempted to alter, manipulate and or misinterpret facts in a way to mislead and misinform those who would read only the division's version without independent review of the actual facts. Severe and serious procedural errors were undertaken by the division to adversely affect the company's device clearance and to finally deny its de novo. The company therefore respectfully urges the commissioner to fully read the meeting minutes agreement Q140104/S001/A003 to understand the extent of the problem created by the division through such severe and serious procedural errors.

d. In its March 26, 2018 letter, the division introduced 7 (seven) deficiencies under Mechanism of Action referring to histology studies present in the submission. Of these, the de novo denial mentions only #5 which is discussed as above and more comprehensively addressed in the company's response to the deficiencies (see Q140104/S001 confirmed received by the FDA on 6/4/18). As discussed in the company's comprehensive responses, the deficiencies were formulated by altering the original meaning of the company's submission without which the deficiencies #1-7 could not have been formulated in the first place. For e.g. the division used the background literature provided by the company where no evidence of selective elimination of unmyelinated axons existed to question why the same parameters *are not used* in the

device settings, while seriously omitting the fact that selective elimination of unmyelinated axons is found only with the device but not in the background literature. *The division therefore undertook to conduct an off-centered review basing its reliance on the irrelevant parts of the background literature rather than to conduct a review of the device itself for its novelty, safety and effectiveness that were not found in the published literature and not found in other devices.* For e.g., in deficiency #1 and #2, the division stating the device's power settings incorrectly (alteration of the original meaning of the submission), uses the term *irradiance* which is a derived, calculated parameter found in the supporting literature that does not apply to Srilas 7 and asking why those settings are not used in Srilas 7 (see Q140104/S001 p20, 21) . Under deficiency #2, again following the two beam radiation found in the literature (but not in Srilas 7), the division asks why the same setting is not being used. The answers to these questions are simple enough that the supporting literature show no evidence of selective elimination of unmyelinated axons and therefore these deficiencies have no relevance to Srilas 7. In yet another example, the division basing its review on sections of the background literature that have no relevance to Srilas 7 (deficiency #6), was asking for tests and evidence for the *opposite effect* of device's mechanism, namely axonal growth. Srilas 7 is an ablation device, while ablation is the opposite of growth or regeneration.

e. The division, while stating it could not understand the electron microscopy images showing myelinated and unmyelinated axons in one instance, was found to be identifying the same structures without any difficulty in another instance only to generate a new deficiency (see meeting minutes disagreement Q140104/S001/A003 p25-28).

f. The device's EM study was performed by the most qualified researchers at the nation's finest research institution of national and international importance and under that institution's own grant funding. The chief research scientist of that institution has unequivocally concluded the ability of Srilas 7 to selectively eliminate only the unmyelinated axons while preserving myelinated axons and non neural (or healthy) tissues, these effects being consistent with the device's IU and IFU statements (see submission's EM study p129). The study outlines among other things, why longitudinal sections are better suited than cross sections (submission p134-135). The division, while ignoring the quality research findings of the EM study was also found to discredit the entire EM study through alteration of the original facts of test parameters used in the EM study. For e.g., deficiency #7 was egregiously formulated by first altering the test parameters found in the submission's EM study and then claiming that the EM study parameters and device settings were not the same (see company's presentation in "Request for Submission Issue meeting" Q140104/S001 p133-137). When the company's presentation on "Mechanism of Action" brought this to the division's attention during the August 6, 2018 meeting, the division brushed it off as being unintentional. The division's response also appears on its meeting minute edits as follows: "The FDA explained that any misinterpretations were not intentional." This statement however does not account for an entire deficiency and other deficiencies being generated by first altering the original meaning of the company's submission. Nevertheless, it's an admission by the division that deficiencies related to the histology (deficiencies #1-7) were formulated by misinterpretation whether intentional or unintentional. It follows, as it would be clear for any reasonable person, when the correct information already provided the company is applied, without alteration of the original facts of the submission, the division did not require cross sections. These facts supported by written evidence should further allow the

commissioner to find that the company's histology tests were more than satisfactory and conforming to device's IU and IFU statements.

5. **The division created a document trail for Srilas 7 potentially portraying the device to be unsafe, high risk and harmful to patients through misstatements, serious omissions and unfavorable decisions that are not based on facts.** These instances elucidated below, indicate severe and serious procedural errors within the division's review process which have adversely affected and continue to undermine the credibility of the company's device and its device submissions.
    a. Escalation of the device risk level without substantiation. As mentioned above, the division used the "de novo" heading and automatic Class III definition to push Srilas 7 as a high risk device, although technological characteristics indicated that Srilas 7 was lower than low level laser and safer than acupuncture needle placements. This unjustified escalation of a device risk to a higher level without basis of fact indicates the inappropriate use of the de novo classification wherein the division defined Srilas 7 to be a high risk and serious risk only because it was under a de novo and not because the device was truly a high risk or serious risk. These instances are further explained below:
        i. In 2012, when Srilas 7 was filed as a 510k, the division indicated that the device is a low level laser and to find appropriate predicates that resemble low level lasers. As mentioned earlier, the company was unable to find a suitable predicate since Srilas 7 was lower than low level laser and hence filed a de novo request.
        ii. In the de novo review and as reflected in the division's 4/18/13 letter, suddenly, Srilas 7 had been turned into a high risk or serious risk device. For e.g. the 4/18/13 letter from the division incorrectly states the device's pulse energy to be in the Joules which is 1 billion times more than the actual pulse energy of the device. **Srilas 7's pulse energy is no more than 1 nanoJoule or 10^{-9} of a Joule**. In the same letter, the division escalates the device risk classification under software to be a serious risk referring to the output energy noted in Joules in the previous deficiency, which as mentioned above is incorrectly stated as being a billion times higher.
        iii. In its 4/18/13 letter, the division notes that Srilas 7 may result in collateral damage and damage to critical neural elements, these being the well-known adverse effects of RF devices and other high energy ablation devices and not characteristic of low level lasers. If Srilas 7 was lower than low level lasers then how does the division justify the high risk and serious risk designation? More importantly, if Srilas 7 has pulse energy in the Joules and would cause collateral damage and damage to neural elements i.e. affect both myelinated and unmyelinated axons then should it not be placed under the 510k pathway and not under the de novo? Fundamentally basic and logical questions have therefore been ignored by the division while formulating its deficiencies. These instances clearly indicate the division's severe and serious procedural errors, especially the off centered review process, wherein the device review was performed using "nonspecific" classification headings. Instead of looking at the device first to assess its specific properties and then to strategize the risk level, the division undertook to rely on nonspecific properties common to other ablation devices and then erroneously apply those general properties to undermine the specific characteristics of the device under review.

b. Substantive feedback and corrective actions are often absent in the division's review process, even when the right information about device safety was provided and pointed out by the company. The division then finds inventive ways that are neither consistent with science nor with regulatory guidelines which continue to place Srilas 7 in a high risk or significant risk (SR) category. These are explained as follows:

   i. In 2014, the company met with the division and provided comprehensive information about Srilas 7's safety indicating that the device fell under NSR or non significant risk whether for a study or otherwise. Furthermore, the company noted that its device was lower than low power lasers and that low power lasers in the treatment of pain are considered as NSR devices per FDA's own guidance documents. In response, the division shifted the significant risk to the needle with unsubstantiated safety concerns continuing to place the device in a significant risk category. (see Table 2b above, see submission p30-31). If the needle is the only safety concern which is inserted like an acupuncture needle to the same anatomical target, then the device should be in 510k, not a de novo. However, the division alters the original meaning and characteristics of device use by noting, the Srilas 7 needle probe could be placed in the neuroforamen (unrecognized malposition, see copy of division's letter dated 10/17/14 p45-46) when in fact needle based ablation devices are to be used only by trained individuals capable of placing those needles correctly. *Statements of this type attempt to implicate the device manufacturer to be responsible for malpractice as well, in this case from incorrect or malposition of the needle probe resulting through improper use of the device, while such use is not covered by the device's IFU statements.* In the same letter, the division notes "chronic neuropathic pain" may result from repetitive needle movement, a speculative adverse effect associated with acupuncture needles while chronic neuropathic pain is the result of "increased" unmyelinated axons, the opposite effect of Srilas 7. As previously elucidated, the Srilas 7 needle placement, not requiring repetitive placements is safer than that of acupuncture needle placements.

   ii. The company appealed the above decision along the supervisorial chain on 11/17/2014 but was unsuccessful. Here too, the appeal decision (January, 2015) was focused on nonspecific generalized use of the device on spine noting "if therapy is delivered on spine" then it would be a significant risk, although Srilas 7 use on spine was safer than FDA's own example of a nonsignificant risk use on spine. see Table 2ba above. See p31-33 of submission). The appeal decision was erroneous with serious omission of facts, since a device's spinal placement alone does not qualify the device study to become a significant risk without the elucidation of what those risks may be. The decision notes 10 different items, the company presented for logical reasoning that Srilas 7 would not constitute a significant risk but most egregiously leaves out the fact that 2 million needle based spinal procedures are being done annually in the US on patients which include the elderly as well as pre-mature babies without any safety concerns (see submission p36-38). Secondly, the decision ignores FDA's own guidance document (UCM126418) wherein Srilas 7 can be determined to be much safer than FDA's own non significant risk device use on the spine. The appeal decision indicated that if the company is not satisfied with the decision, it should appeal to

the commissioner as the next step. The company placed an appeal to the commissioner in 2015 awaiting a response.

iii. In its de novo DEN 170050, the company had noted, how it was extremely important for the division to first understand the device's safety characteristics. The company brought the risk designation problem in the cover letter of its de novo submission (p5-18), as well as allocating a separate chapter in the submission (p58-90). Furthermore, a number of tables, figures and also a presentation was included demonstrating that Srilas 7 was much safer than NSR devices found in FDA's own guidance. When the division's deficiency letter was received on March 26, 2018, the company noted as explained earlier in this petition, that there was no mention of the significant risk vs. non significant risk in the entire 16 page deficiency letter, although the risk designation for Srilas 7 was a chief concern in the company's submission and the company had specifically requested that the division address that. The company then contacted the division in its e-mail of 4/2/18 why the NSR designation was missing. In response, the division noted the following (see 'Request for Submission Issue meeting' Q140104/S001 p 232): "A significant risk decision is normally not a part of the DeNovo review, and no consideration was made for SR vs. NSR for future studies in this review. So any prior decision about SR determination still represents the Center's current thinking." However, a month later, the company received a letter dated May 7, 2018, whereby another FDA division appeared to have taken up the company's appeal that was pending review by the commissioner. The appeal decision was rendered without the knowledge of the company and its participation. The appeal was therefore conducted unilaterally and without the company's input. The May 7, 2018 letter states "a meeting would not aid in the matter" (see 'Request for Submission Issue meeting' Q140104/S001 p233). The decision reflected in this letter which upholds the January 2015 decision was again arrived through serious omission of critical facts and by neglecting FDA's own guidance. This decision of May 7, 2018 is not a proper adjudication of the appeal, since the company was not afforded even the basic due process rights, while the decision circumvented the appeal process before the commissioner.

iv. Appeal process through the division's supervisorial chain under §10.75 is seriously flawed or nonexistent. This fact is illustrated in the following examples.

    1. The January 2015 appeal decision ignores the fact that the FDA guidance document UCM126418 specifically provides an example of a "non significant risk" (NSR) use of a device on the spine wherein, the device is placed on exposed spinal cord after breaching the spinal canal. The latter guidance is consistent with the annual procedure data available in US which indicate millions of procedures being performed annually with spinal needles, wherein spinal needles are *deliberately* placed into the spinal canal or into the neuroforamen and therapy delivered. The Srilas 7 needle placement on the spinal facet joint is no different than over a million (around 1.9M) of such needle placements done annually in the US alone, to the same anatomical targets or the facet joints by similar probes and needles. One does not need to be a legal expert, scientist or a physician to conclude that, if a device does not create a condition where

breach of spinal canal happens in the first place, then its use on the spine would be an NSR. Secondly, with respect to Srilas 7, the laser emission has already been deemed safe by the division (see letter of 10/17/14, see submission p45-46) and hence there's no logical reason for upper level decisions not to follow FDA's own published guidance and conclude that <u>*although*</u> the Srilas 7 needle probe is used on the spine, it does not breach the spinal canal, is not placed in the neuroforamen, leading to the obvious conclusion that Srilas 7 would be a non significant risk device. The January, 2015 appeal decision concluding the *opposite* of a naturally arrived, fundamentally logic conclusion, failed in its very purpose for which it was instituted under §10.75.

2. The company described earlier, the strange premises on how the May 7, 2018 appeal decision came into existence. Perusal of this decision letter indicates that no part of the FDA guidance document, UCM126418 has been used in arriving at its decision. It can be seen that the letter lays improper ground work in order to arrive at its flawed decision. On page 2 (see copy of this decision letter in "*Request for Submission Issue meeting" Q140104/S001* p234), the letter notes, "Your submissions also reference pain associated with invasive procedures such as needle sticks. C Laser's appeal suggests that temporary numbness, pain, and weakness may result from treatment with the Srilas 7." These statements are an alteration of the original facts of the submission, since temporary numbness, increase in pain and weakness are the side effects of RF ablation and not Srilas 7, while needle sticks themselves are common to all needles not just to Srilas 7. The letter then formulates its conclusion on page 10, based on its alteration of the original meaning of the company's submission as follows: "Further, C Laser has conceded numerous risks associated with the use of Srilas 7, including, for example. (1) pain resulting from any invasive procedure such as a needle stick and the risk of injury resulting from mechanical impact during needle insertion; (2) temporary numbness, temporary weakness. temporary increase in pain, and other temporary adverse events potentially resulting from the proposed use of Srilas; and (3) increased pain." Contrary to these conclusions, Srilas 7 is devoid of adverse effects and side effects, while nowhere does the company concede or admit to having numerous risks for its device. Hence the conclusions reached in this letter are egregiously misleading, since besides altering the original meaning of the company's submission, they purport to convert every needle stick as a significant risk device, for e.g. home glucose monitors, flu shot needles, home use insulin needles etc.,. The decision lacks any policy guidance and does not refer to FDA's guidance document UCM126418 necessary to adjudicate in a comparative fashion whether or not Srilas 7 is more safe as compared to "non significant risk" examples provided by the FDA including such examples of device use on spine.

In light of the evidence presented, the commissioner is respectfully urged to find the January 2015 appeal decision and the May 7, 2018 decisions to be

inconsistent with FDA's own guidance and improperly adjudicated under §10.75. The decisions considered only the division's interpretations, which in turn as described above were erroneously based on alteration of the original facts of the submission. The commissioner is respectfully urged to consider the strong evidence presented by the company here. He should therefore overturn these improper and illogical appeal decisions, declaring Srilas 7 to be a non significant risk (NSR) device whether for a study or otherwise.

v. The de novo denial letter states the aforementioned January 2015 appeal decision (wrongly noted in the denial letter as being July 2015, no decision was rendered in July 2015) and the May 7, 2018 letter as the basis for future studies in US to be a significant risk study mandating an IDE submission, although as mentioned above and further elucidated in the company's responses, both these decisions were arrived through serious omission of facts and through alteration of the original facts of the submission. Both decisions are improper adjudications of an appeal since established FDA guidance and national standards for device use have been ignored. The May 7, 2018 decision indicates that even minimal due process rights were not afforded to the company.

The above instances indicate the division's serious and severe procedural errors, where checks and balances are absent within the division, while the ability of the division to influence its supervisorial chain happens to be enormous. Upper level decisions are rendered relying on information provided by the division rather than an independent review of the actual facts. A proper independent review of why Srilas 7 would not fall under an IDE is found in the submission (see p 36-38 'Expert opinion on the conduct of a significant risk study on a low risk or no risk device').

c. Warning letters related to the study inspection site were not related to the study, but related to administrative errors within the local FDA branch responsible for document handling and forwarding. The FDA Office of Device inspection (ODI) conducted a routine inspection of the study site and the IRB in September of 2013. The inspection in part was driven by the misleading information in the division's 4/18/13 letter indicating the study would be a significant risk study. The inspection found that the study had concluded on 4/18/13 in compliance with division's determination, although neither the company nor the study IRB agreed with that determination, which as elucidated above was arrived by the division's seriously erroneous review methodology. Additionally, the inspectors found no patient harm or safety concerns related to the device. Moreover, they also inspected the procedure room which was the same room found in the procedure video given to the FDA as part of the company's submission. The inspectors also commented that the facility was clean and spotless as opposed to some of the other facilities they had inspected. The inspectors did give out deficiency letters finding errors in documentation and organization of the management structure. The company agreed to provide three sets of documentation indicating administrative corrective actions unrelated to patient care, for e.g. data on patients who received care with the device as a medical necessity after 4/18/13 but were not enrolled in the study. The documentation was required to be sent to the local FDA branch. The first set of documentation reached the local FDA branch without any problems. However, the second and the third set returned as undeliverable after the registered mail failed to deliver multiple times. Copies of the returned mail covers marked as "undeliverable" by the post office are attached with the supporting documents for the commissioner's perusal. These covers demonstrate the

multiple attempts undertaken by the post office to deliver the documents to the local FDA branch and failed to do so. When the 2nd and the 3rd set of documents were not received, it triggered the warning letter from FDA's ODI, since the company appeared to be noncompliant with the document requests and corrective actions. Subsequently, these discrepancies were clarified and all requirements of the inspection including the documentation were deemed satisfactory to the FDA (see letter from ODI). *The de novo denial mentions these warning letters attempting to connect them with the clinical data provided by the company, when the warning letters are not related to the clinical data provided and did not change the device's clinical effectiveness and safety as reported. As mentioned above, the genesis of the warning letters has no relation to the current de novo submission.*

In summary, the information above and the instances described therein, supported by written evidence demonstrate the creation of a document trail by the division based on statements and decisions that have no factual basis. They are intended to discredit and demean the device characteristics and its submission by altering the original facts through misstatements and serious omissions along with unfavorable decisions that are based on those altered facts and serious omissions. These instances are then used to prevent the natural progression of the device to its clearance. Finally, the created document trail is intended to mislead and misinform those who would read or consider only the division's version without an independent review of the actual facts.

6. **The division's clinical study requests apply to drug based investigations looking for a systemic effect and not to devices that act locally on focal anatomical areas that have no systemic effect**.
    a. For the de novo submission, the IFU does not include an indication to treat or diagnose a disease. As mentioned earlier in this petition, the IFU does include the same statement the FDA made in 2010 that the device is indicated when: *"no approved alternative exists for patients with uncontrolled pain using currently available treatment, or for patients who are contraindicated for pain medication."* Consequently, the clinical data presented is consistent with that statement i.e. patients who failed currently available treatments have improved on being treated by the device. In other words, the device Srilas 7 was effective where other treatments failed for the same pain symptoms. Srilas 7 is a not a first line therapy. It's not a second line therapy. It's a 3rd line therapy only applicable for patients who failed conservative, injection or other non-ablative treatments. Such indications are the same for use of approved needle based RF ablation devices (e.g. NT1000).
    b. RF ablation devices although used as a 3rd line therapy has an FDA IFU statement as "a device that creates neural lesions," this neural lesion affecting all nervous tissue whether it be myelinated or unmyelinated. Srilas 7 used in the same fashion affects only the unmyelinated axons. Both devices address focal pain symptoms in the periphery at the source of pain and do not address systemic pain or pain pathways. On the contrary, drug based treatments such as oral pain medications cause reduction through a systemic effect. While a randomized control trial including a large group of participants is applicable to drug based treatments, the same is not applicable to devices that perform focal ablation restricted to a very small area of application namely the contact area of a needle tip. In fact, RF ablation studies when randomized have resulted in no useful data and show that ablative treatments are NO better than conservative treatments since it was performed on patients who did not require the RF treatment in the first place. This information has been

specifically pointed out through graphical and illustrative figures in the company's submission.

c. The company attached recent and historical literature to support this fact, i.e. randomized controlled trials are inapplicable in the assessment or usefulness of ablation devices since patients have to fail 1st line and 2nd line treatments in order to be subject to needle based ablative devices such as RF and Srilas 7. Despite the company's clear evidence presented repeatedly to the division, that randomization leads to no meaningful results, the division has made no substantive argument as to why the nationally accepted clinical use of ablative treatments as applicable to patients is wrong and why the device needs to be used on a randomized basis. Hence, the division's requests for study randomization are lacking in clinical rationale and contrary to how an ablation device are used in clinical practice. Along the same lines, the Srilas 7 study followed nationally established study measurements used in the clinical assessment of effectiveness of ablative devices. The division makes a serious omission of fact and does not mention that the study used nationally recognized study measures, instead, it asks that the study use NRS (numeric rating scale) for pain assessment which is applicable to drug based assessment of pain relief and pain reduction. These instances indicate the division's profound lack of clinical reasoning and or a serious omission of critical facts to generate deficiencies that would not otherwise be generated, if the correct information were applied first. The commissioner should consider these facts, supported by written evidence to recognize that the device Srilas 7 is consistent with its IFU statements. Its use as a needle based ablation device in clinical practice is the same as the clinical use of RF devices and that it benefits patients who have failed 1st line and 2nd line therapy. Accordingly, the commissioner should recognize that the study would not be randomized, but would be applicable in patients where *no approved alternative exists for patients with uncontrolled pain using currently available treatment, or for patients who are contraindicated for pain medication."* As noted above, this statement is consistent and the same with what was noted by the FDA in 2010.

d. The company pointed out under 4-e above of this petition, how the division while claiming that histology images are not interpretable in one instance was found to comprehend those images in another instance only to generate a new deficiency. Along the same lines, the division claiming that the clinical study measures were incomprehensible was found to comprehend small improvements noted in steroid based injections in 5 patients, while ignoring the substantial and significant improvements noted in 22 patients who were subject to Srilas 7 using the same study measures (see "*Request for Submission Issue meeting" Q140104/S001* p10-12). These instances demonstrate the seriously erroneous review process but more specifically, the arbitrary and capricious nature employed by the division, wherein information is comprehensible when it leads to the generation of a deficiency but not when it supports the device's effectiveness.

7. The following instances indicate that the division's suggestions can potentially cause patient harm than benefit.

a. In 4 (d) above, the company demonstrated how the division focused on irrelevant aspects of the supporting literature, thereby performing an off-centered review to generate major deficiencies. During the meeting of August 6, 2018, the division stressed how the device's mechanism can only be understood if the power settings are increased to an astronomical level of 10^{11} W/cm^2. The company indicated that those setting would cause severe harm to patients such as the destruction of the entire sciatic nerve and not

compatible with human life. In a separate e-mail on August 15, 2018 (see DEN 170050/S001 *Company's Final Response to Deficiencies* p30), the company re-emphasized to the division that the aforementioned settings constitute a Giga watt laser or 100 billion times more powerful than a Watt laser. Giga watt lasers would likely include military applications where entire structures may be completely be destroyed by the use of such powerful lasers.

b. In 6 above, the company demonstrated how the division's clinical study suggestions are not consistent with nationally established guidelines for the proper use of needle based devices and consequently, inconsistent with the clinical study of such devices. In deficiency #9, FDA suggests that study patients who already failed steroid based injections receive an additional round of steroid injections. This suggestion is contrary to the distinct warning/cautionary note in CMS standards (submission p289) when using steroid injections to treat facet joints (the anatomical target) in patients. The standard reads as follows: "appropriate consideration is given to the adverse effects (e.g., adrenal suppression of corticosteroid injections)" implying the need for ablative treatments as the next step in patients who failed steroid injections. The division's suggestion, that a second round of steroids be given to patients who already failed steroid injections before they receive Srilas 7, a needle based ablative treatment is contrary to nationally established clinical standards and would cause patient harm if followed.

The above instances supported by written facts indicate that the division's review process are seriously erroneous. The above suggestions made by the division are not only intended to prevent the device's meaningful progress in the de novo review process, but if followed may also cause various degrees of harm to patients. For e.g. the use of extremely high powered lasers, repeatedly advocated by the division, would cause irreversible patient harm and has no place in medical devices intended to be applied directly on patients.

8. The division's requests for non-clinical performance testing are misleading and lacking substantive feedback on questions and deficiencies already addressed by the company. The de novo denial lists the same deficiencies in a cyclic fashion being nonresponsive to the information given by the company.

    a. Biocompatibility tests: The company had noted that the Srilas 7 needle probe is only a proprietary assembly of existing 510k needle and 510k fiber that does NOT change the chemical and physical properties of those approved needles and fibers. The division has therefore not made a case for new biocompatibility studies since there is NO change in the properties of the individual but approved components that have already passed the relevant tests. The division must first indicate what possible new information it expects to find when there is no change in physical and chemical properties of the individual components already tested for biocompatibility as approved 510k devices.

    b. Sterility and Shelf Life: The division is erroneous in noting the major packaging manufacturer used by the company has not done an aging study when in fact data provided by the manufacturer shows that it has been. This manufacturer and his packaging have been used for a number of approved medical devices. As mentioned in 'a' above, the device's needle probe does not change the physical or chemical properties of the individually approved and tested 510k components and therefore new aging tests specifically for the company's device are NOT required.

    c. EMC Testing: Comprehensive EMC testing conforming to all applicable standards have already been performed on the device by nationally accredited laboratories and engineers.

The purported "voltage dips to proximal RF emitters" noted in the de novo denial is NOT applicable to Srilas 7 as it has no such emitters.

d. Electrical Safety Testing: Contrary to the claims made in the de novo denial letter, that this information was not found, it is present in pages 333-547 of *Comprehensive Response to Deficiencies and Request for a Meeting* Q140104/S001 (confirmed received by the FDA on 6/4/18). This is another example of the division's serious omission of facts, found in plain sight, indicating the ongoing erroneous review process on which the de novo denial is based on.

e. Software: As described above, the software has been escalated to higher risk without basis of fact. The risk level determinations pursuant to established IEC standards have resulted in the device being a very low or a "no" risk device and the same applies to any software found in the device.

In summary, the division is using the "de novo" classification headings to demand tests that provide no useful information, but to increase the filing burden on the company.

9. Division's review timelines and conduct of meetings consistently violate established regulations affecting basic due process rights afforded to any company. These instances are described below.

   a. The company's de novo submission DEN 170050 was confirmed received by the FDA on 9/19/17. It's mandatory by law that FDA must make a classification determination for the device that is the subject of the De Novo request by written order within 120 days of the request (see section 513(f)(2)(A)(iii) of the FD&C Act). However, no response was received by the division past 180 days. This then led the company filing for '*Missed MDUFA Decision communication* (DEN 170050/A001) for lack of final decision or feedback 180 days past the submission. Along the same lines, after all final responses were confirmed received by the FDA on 9/18/18, the division exceeded the mandatory 120 days and well over 180 days to render its de novo denial order only on 4/3/19. These explicable delays along with the seriously erroneous review process described above indicate that the division consistently ignored established regulations and FDA's own guidance documents, when adjudicating the device submission.

   b. The request for submission issue meeting was held on August 6, 2018. On this day, the company was to get 1 (one) hour meeting time to present its histology tests under "Mechanism of Action" and show how the clinical translation had already taken place. However, the division wanted to make its own presentation to the FDA members as a rebuttal to the company's presentation. Although, the division had a copy of the company's presentation, the division made no attempt to provide a copy of its presentation to the company despite company's request for the same and thus reducing the preparedness of the company to respond to questions. On the day of the meeting which would start at 9 am, the company was escorted late to the meeting. As a result, the company was unable to properly set up its computer equipment and demonstrate its video of how the device works in humans and dogs. The above information can be readily verified through the meeting minutes where it states that the meeting started at 9:08 am instead of 9am. The 8 minutes could have been utilized for showing the company's video. As the company's presentation (which was already shortened to accommodate the division's presentation) progressed, the division interrupted to cut short the company's presentation to start its own presentation. The division could not complete its presentation either due to time constraints with the meeting room evacuated for the next in line. These facts could be readily verified in the company's meeting minutes disagreement (*Q140104/S001/A003*) which strongly point out how the division conducted

the meeting, but more importantly, purported to include "add-on" information that were never part of the August 6, 2018 meeting.

c. On November 2, 2018, the division (not the company) requested a teleconference. However, as in the previous instance above, the division did not disclose what the meeting was about. Later, its e-mail communication indicated that the teleconference was to discuss the device's IFU. However, instead of discussing the specifics of the device's IFU, the division went on to read out the same deficiencies found in its March 26, 2018 Additional Information (AI) or deficiency letter and as if the company had made no response to those deficiencies. The company pointed out that it had already provided comprehensive responses while the division is just repeating the same deficiencies without a substantive argument on the responses already provided. Since all information is already present in the company's filings, the company requested that the division provide scientific rationale and logical reasoning for any new tests, e.g. towards the need for cross sections or a new clinical study. The company noted that the division has provided no such scientific rationale or logical reasoning to date, to justify the need for any additional data.

The above instances supported by company's filings, written communications and recorded meetings (Nov 2, 2018) readily indicate the significantly disadvantaged position the company has been placed in, whereby even minimal due process rights have not been afforded to the company. These examples should further assure the commissioner that this petition and the actions requested by the petitioner therein are more than justified and should be granted.

10. The division did not afford expedited review, although the device qualified for the same by FDA's own written communication.
    a. In 2010, the FDA provided written communication that the device qualified for expedited review since it was in "patient's best interest" and applicable to patients who had *no approved alternative exists for patients with uncontrolled pain using currently available treatment, or for patients who are contraindicated for pain medication.*
    b. In 2017, when the company requested for an expedited review, the division indicated that it should have been done before the submission of de novo application and not with it.
    c. In 2018, the FDA commissioner made a public announcement that breakthrough devices especially in the treatment of local pain syndromes (similar to Srilas 7) do not need a separate application but can be considered breakthrough (in patient's best interest) during the review process. The division did not respond even when the company attached the commissioner's announcement and requested that the device be considered for expedited review and clearance.
    d. Srilas 7 is a breakthrough device in the best interest of the patient. Under its technological innovation pain relief and functional improvement is possible without adverse effects or side effects even in disabled patients who have failed other modalities of pain treatments.
    e. Srilas 7 may be a significant and useful device in reducing the opioid crisis facing this nation.
    f. Srilas 7 may be a significant and useful device in reducing focal pain and focal pain related disability in military personnel who have been injured in the line of duty and have failed to improve with approved treatments modalities. Srilas 7 has been effective in reducing or eliminating chronic pain and pain related disability in law enforcement officials and firemen who have been injured in the line of duty and had failed previous treatments with approved modalities.

For all of the aforementioned reasons, the commissioner should consider that Srilas 7 is in the best interest of the patient. Accordingly, he should reverse the denial order and afford clearance to Srilas 7.

11. Abandonment of the least burdensome approach in the device review process mandated by congress and passed in to law. The instances described earlier indicate that the division ignored fundamental, basic and critical data provided by the company, all the while asking for more tests and data that provide no useful information. The division's review methodology along with its erroneous review process is anything but a least burdensome approach. These instances are described below.
    a. Risk based assessment under the least burdensome approach: The division abandoned the principles of least burdensome approach, ignored the fact that the device's laser emissions were less than that of a laser pointer and that its needle placements were safer than acupuncture needle placements. The minimum inference under the least burdensome approach was that Srilas 7 was safer than other 510k needle based devices. The least burdensome approach if followed would have immediately removed Srilas 7 from Class III to be placed in at least Class II if not in I.
    b. Mechanism of action under the least burdensome approach: The division abandoned the principles of least burdensome approach by requesting new tests i.e. cross sections, when existing EM studies showed all information consistent with the device's indication for use (IFU). These EM studies conducted in one of the most prominent research facilities in the US and certified by the most qualified specialists as being consistent with the device's IFU, exceeded the minimum standard of proof required under the least burdensome approach. This test along with 3 other animal tests conducted by the company substantially exceeded the minimum requirements needed under the least burdensome approach towards the device's IFU.
    c. Clinical data under the least burdensome approach. Clinical data presented by the company were substantially superior and exceeded minimum requirements since the company demonstrated effectiveness in human and dogs that had intractable pain and disability from the same. The proof that was presented did not just include clinical data, figures, graphs and statistical analysis on 95 patients disabled by focal pain symptoms but also video evidence of clinical improvements in 20 (twenty) different patients and 2 (two) dogs. The statistical analyses show the clinical study to be extremely strong with a statistical sample size $n = 830$ and by demonstrating improvement on two variables, namely, focal pain and focal pain related functional disability considered simultaneously, through repeat and periodic assessments (see company's presentation in Request for Submission Issue meeting" Q140104/S001 p155-212). The evidence presented therefore far exceeded those found with similar but approved needle based devices intended to be used in the same manner as Srilas 7.
    d. Non-clinical testing under the least burdensome approach. All testing were conducted in nationally accredited laboratories by specialist engineers. Where applicable, the company submitted information on 510k devices incorporated in its device. Under the least burdensome approach new testing was not required. The device safety controls also far exceeded those of approved 510k devices.

In light of the comprehensive and factual information provided in this petition, supported by strong written evidence, the commissioner is respectfully urged to reverse the denial order, remove Srilas 7 from automatic Class III and afford clearance for the device. In addition, he should declare the device study to

be of non significant risk (NSR) consistent with established FDA guidance, since the device use is safer than FDA's own examples of non significant risk studies. Finally, consistent with FDA's earlier determination for an expedited review, the commissioner should declare the device Srilas 7 to be a breakthrough device in the patient's best interest towards any future submissions including newer indications.

Respectfully submitted,

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