Risk Assessment Report

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Table of Contents

Risk Analysis: Intended Use/Misuse 3
Hazard Traceability Matrix 7
Risk Evaluation 10
Risk Evaluation Matrix 10

Risk Analysis: Intended Use/Misuse

The nerve cap is a surgical implant that is a tubular device with one open end and one closed end (cap) designed to provide protection for a peripheral nerve end or stump where repair is unattainable or undesired. The device is intended to fit over and bond to the peripheral nerve end to isolate it from the surrounding soft tissue bed by pulling the nerve into the cap and bonding the luminal surface of the cap to the epineurium via photochemical tissue bonding (PTB) technique. The distal end of the cap has a suturable tab to allow the surgeon to suture the device to surrounding tissue.

The nerve cap is intended to protect a peripheral nerve end and to separate the nerve end from the surrounding environment to reduce symptomatic nerve end neuroma following a traction neurectomy. This product is intended for use by trained medical professionals.

The nerve cap is derived from a bovine source and should not be used for patients with known sensitivity to bovine derived materials. The nerve cap is contraindicated for use in any patient for whom soft tissue implants are contraindicated; this includes any pathology that would limit blood supply and compromise healing or evidence of a current infection.

The nerve cap should not be implanted directly under the skin. This product is not intended for use in vascular applications. This product is designed for single use only; do not re-sterilize the nerve cap. Discard all open and unused portions of the product. The nerve cap is sterile provided the package is dry, unopened, and undamaged. Discard the product if mishandling has caused possible damage or contamination, or if the product its past its “Use-by” date.

This product is not intended to be sutured to the nerve end. This product is not intended to be photochemical tissue bonded to any body tissues other than peripheral nerve. Avoid crushing, crimping, kinking, or other damage due to application of surgical instruments (e.g., forceps, needle holders, scissors, etc.) during handling of the device. Always handle the nerve cap using aseptic technique. Do not trim the distal tab of the cap prior to implantation.

International Standard ISO 14971:2012: Medical devices — Application of risk management to medical devices. Annex C: Questions that can be used to identify medical device characteristics that could impact safety:

C.2.1: What is the intended use and how is the medical device to be used?

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C.2.2: Is the medical device intended to be implanted?

Yes, the product is intended to be implanted in the patient’s upper limb at the site of the peripheral nerve end.

C.2.3: Is the medical device intended to be in contact with the patient or other persons?

Yes, the nerve cap is a permanent implant.

C.2.4: What materials or components are utilized in the medical device or are used with, or are in contact with, the medical device?

The product is manufactured using decellularized, glutaraldehyde-treated bovine pericardium. The surface area of the device which is intended to bond to the nerve end is stained with rose bengal (4,5,6,7-tetrachloro-2',4',5',7'-tetraiodofluorescein).

C.2.5: Is energy delivered to or extracted from the patient?

No.

C.2.6: Are substances delivered to or extracted from the patient?

No.

C.2.7: Are biological materials processed by the medical device for subsequent re-use, transfusion or transplantation?

No.

C.2.8: Is the medical device supplied sterile or intended to be sterilized by the user, or are other microbiological control applicable?

Yes, the product is supplied sterile and is intended for single use.

C.2.9: Is the medical device intended to be routinely cleaned and disinfected by the user?

No.

C.2.10: Is the medical device intended to modify the patient environment?

No.

C.2.11: Are measurements taken?

No.

C.2.12: Is the medical device interpretative?

No.

C.2.13: Is the medical device intended for use in conjunction with other medical devices, medicines or other medical technologies?

Yes, the product is intended to be photochemical tissue bonded to the peripheral nerve end, which requires the use of a solid-state laser. A potential problem associated with the interaction of the laser and the nerve cap is the failure of the laser to be used correctly in bonding the nerve cap to the nerve end.

C.2.14: Are there any unwanted outputs of energy or substances?

No.

C.2.15: Is the medical device susceptible to environmental influences?

Yes, the packaged product should be kept in a clean, dry location between 10 – 30°C.

C.2.16: Does the medical device influence the environment?

No.

C.2.17: Are there essential consumables or accessories associated with the medical device?

No.

C.2.18: Is maintenance or calibration necessary?

No.

C.2.19: Does the medical device contain software?

No.

C.2.20: Does the medical device have a restricted shelf-life?

Yes, the product has a shelf-life of 32 months. The “Use-by” date is specified on the package and is in the form Year-Month-Day.

C.2.21: Are there any delayed or long-term use effects?

No.

C.2.22: To what mechanical forces will the device be subjected?

The product will be subject to the pressures that soft tissue of the peripheral limbs is normally subjected to.

C.2.23: What determines the lifetime of the medical device?

The nerve cap is a permanent implant that is intended to integrate with the surrounding tissue.

C.2.24: Is the medical device for single use?

Yes.

C.2.25: Is safe decommissioning or disposal of the medical device necessary?

The product or any unused portions of the product should be disposed of according to institutional guidelines for biological waste.

C.2.26: Does installation or use of the medical device require special skills?

Yes, the product is intended for use by trained medical professionals; specifically, implantation of the nerve cap requires a surgeon.

C.2.27: How will information for safe use be provided?

Information will be provided directly to the end user (i.e., the surgeon) by the manufacturer.

C.2.28: Will new manufacturing processes need to be established or produced?

No.

C.2.29: Is successful application of the medical device critically dependent on human factors such as the user interface?

No.

C.2.30: Does the medical device use an alarm system?

No.

C.2.31: In what way(s) might the medical device be deliberately misused?

None.

C.2.32: Does the medical device hold data critical to patient care?

No.

C.2.33: Is the medical device intended to be mobile or portable?

No.

C.2.34: Does use of the medical device depend on essential performance?

No.

Hazard Traceability Matrix

According to ISO 14971, risk is defined as the combination of the probability of occurrence of harm and the severity of that harm. To categorize severity of the potential harm for the medical device, the appropriate descriptors in Table 1 are used:

Table 1. Severity

Rating	Definition	Value
Critical	Requires explant surgery	5
Serious	Chronic immune response/pain	4
Moderate	Mild allergic reaction/infection or moderate pain	3
Minor	Acute nerve sensitivity or pain	2
Negligible	Local, mild, transient effects	1

Categorization of probability of the potential harm is given by Table 2. The probabilities are given in terms of per use of the device (i.e., per surgery).

Table 2. Semi-Quantitative Probability Levels

Rating	Quantitative Probability	Value
Frequent	≥50%	5

Probable	<50%	4
Occasional	<5%	3
Remote	<0.5%	2
Improbable	<0.05%	1

ISO 14971 requires that the manufacturer compile of list of known and foreseeable hazards associated with the product, and to consider the reasonable sequence of events that can produce hazardous situations and harm. A hazard cannot result in harm until certain circumstances lead to a hazardous situation. Table 3 provides a list of relationships between hazards, foreseeable sequences of events, and the resulting hazardous situations of harm that can occur for the nerve cap medical device. ISO 14971 does not define acceptable risk; this is left to the manufacturer. Table 3 gives a quantitative measure of risk based on the combination of severity and probability for each harm.

Table 3. Hazard Traceability Matrix

ID	Hazard	Sequence of events	Hazardous Situation	Harm	Severity	Probability	Acceptable
1	Chemical (Biocompatibility)	Implantation leads to allergy/irritation	Immune response to implant material/substances	Irritation, Allergy, Delayed healing, Chronic immune response	5	1	ACC*
2	Residues/contaminates	Product is incorrectly manufactured/sterilized/packaged	Immune response, cytotoxic, infection	Local cell/tissue damage, Infection	4	2	ACC*
3	Loss or deterioration of function	Incorrectly implanted, or device fails/degrades	Recurrence of symptomatic neuroma	Chronic pain	5	3	N ACC
4	Use error	Aseptic technique not used	Possibility of infection	Infection (bacterial, viral, or other agents)	3	2	ACC*
5	Inadequate labelling	Product is implanted in individual with known allergy to product material	Immune response to implant material/substances	Irritation, Allergy	5	1	ACC*
6	Operating instructions	Product was implanted too close to skin, not sufficiently buried in tissue	Protrusion	Wound dehiscence, Explant surgery	5	1	ACC*

7	Insufficient control of manufacturing processes	Product is not manufactured with correct material or sterilization technique	Wrong material or incompatible sterilization technique	Chronic immune response, Explant surgery	5	1	ACC*
8	Incorrect measurement	The cap's size/nerve end diameter was not accurately measured	Friction fitted cap on nerve end	Nerve compression, pain	3	2	ACC
9	Inadequate specification of design parameters	The cap is manufactured with the wrong dimensions/size	Cap is not sufficient length or thickness	Incorrect nerve repair, pain	4	1	ACC*

Table 3 begins by observing the chemical hazard that could be the result of an allergic response or irritation. The severity of this was evaluated at a level 5 due to the harm of delayed healing and possible risk of death. Despite this severity, the probability of this event is ranked at a level 1 because our material is collagen which has been shown to be biocompatible with the body. This makes this an acceptable risk if there is a control in place which means which should investigate efforts to minimize the severity of a chemical hazard to occur. The next hazard is the risk of residue or biological contaminates that may occur if the product is manufactured, packaged, or sterilized incorrectly. This may result in an infection and creates a cytotoxic environment resulting in local cell or tissue damage. The probability of this occurrence is at a level 2 because manufacturing issues do occur but is still not very likely. However, the severity of this evaluated at a level 4 due to the severity of the harm that may be caused by this issue. As a result, this hazard is evaluated as acceptable with a risk control in place. The third hazard is the loss or deterioration of function which is caused by an incorrect implantation or degradation of the device. This hazard will result in chronic pain as the symptomatic neuroma returns. Due to this harm the hazard may cause, this was evaluated at a level 5 severity as it would require surgery to remove it. The probability of this occurring is placed at a level 3 due to the chance that the collagen material may degrade before nerve growth stops. This places the risk as unacceptable as the level of risk due to the severity of the harm and the higher probability of this occurrence. We will need to investigate minimizing the probability of this risk occurring.

Hazard four involves the hazard of user error that may occur is the aseptic technique is not used. Failure to follow the technique may result in the harm of infection posing a threat to the health of the safety. The severity of the hazard is a level of 3 because it poses harm, but through antibiotics and treatment the patient will be healed. The probability of this occurring is at a level 2 because it could happen but is not very likely. As a result, this risk is acceptable with a risk control in place to reduce the severity or probability of occurrence. The fifth hazard involves the inadequate use of labels to warn users of the device and its contents. This risk poses many issues one of which is that the individual implants this device into a patient with an allergy to the material. The device would result in an immune response in the patient and severe irritation. This places this risk at a severity level of 5 but has a probability of 2 in terms of occurrence. As a result, this risk is acceptable with a risk control in place such as increasing the number of labels and their placements. The sixth hazard involves the user not following operating

instructions resulting in the implant not being implanted too close to the skin or not sufficiently buried in the tissue. This may result in severe protrusion of the device and requires explant surgery to resolve. The severity of this issue is at a level 5, but the probability of this is at a level 1 due to the unlikelihood that this would occur. As a result, this hazard is acceptable with risk control in place that would reduce the severity of incorrect placement of the device.

Hazard 7 involves being insufficiently in control of the manufacturing process resulting in the product being manufactured without the correct material or sterilization technique. This hazard impacts the compatibility of the device and can result in a chronic immune response that would require explant surgery to resolve. Due to this, the hazard has a severity of 5, but the probability of this occurring is evaluated at a level 1. This hazard is then acceptable if there are risk controls in place. The eighth hazard involves the hazard of incorrect measurement of the device creating a cap diameter that does not fit well on the nerve end. This will result in friction between the nerve and the cap and may cause nerve compression and pain. Although uncomfortable, the severity of this hazard is at a level 3 and the probability of its occurrence is at a level 2. This places the risk as insignificant and acceptable. Hazard 9 results from inadequate specifications on design parameters in which the cap is manufactured with the wrong dimensions. This would produce a cap with the insufficient lengths or thickness. The patient would then experience pain and the nerve would repair incorrectly. Due to this, the severity of this hazard is evaluated at a level 4 as this pain is chronic. However, the probability of this occurring is at a level 1 which indicates that this event is likely to never occur. As a result, this hazard is acceptable if there is a risk control in place.

Risk Evaluation

The definition of risk according to ISO 14971 is the combination of the probability of occurrence of harm and the severity of harm. We have determined our risks based on our hazard traceability matrix. Also from ISO 14971 risk analysis is described as a systematic use of available information to identify hazards and to estimate the risk. To evaluate the risk associated with each of these hazards we have created a matrix to act as a system of determining which risks are acceptable. Hazards with a high severity of harm and is probable in occurrence are considered unacceptable. Hazards with low severity and low probability are still risks but are acceptable. For the harms that are between the two extremes in severity and probability are also acceptable but are higher risks than low severity, low probability. Our system for evaluation analyzes these risks in a chart that is color coded to show the different acceptability's of risk. The area in red is what we consider unacceptable, for our product the only risk in this section is loss or deterioration of function. The matrix showing each of our risks plotted against probability and severity are shown within Table 4, and color coded to provide how acceptable the risk is.

Risk Evaluation Matrix

Table 4 is a risk matrix where the estimated risks from Table 3 have been entered into the appropriate cells. The cells highlighted in green are defined as an insignificant risk. The cells in yellow are an acceptable risk with the appropriate design control(s) in place. Red is only an acceptable risk with the appropriate design control(s) in place and reasoning as to why it is acceptable. Otherwise, it is unacceptable, provoking a design amendment(s).

Table 4. Risk Evaluation Matrix

		Severity				
		1	**2**	**3**	**4**	**5**
Probability	**1**				9	1, 5, 6, 7
	2			2, 8	4	
	3					3
	4					
	5					