May 31, 2019

Monarch Bioimplants GmbH
Rivelino Montenegro, CEO
Platz 4, Root, 6039 CH

Re: K190246
Trade/Device Name: NeuroShield
Regulation Number: 21 CFR 882.5275
Regulation Name: Nerve Cuff
Regulatory Class: Class II
Product Code: JXI
Dated: January 31, 2019
Received: February 6, 2019

Dear Rivelino Montenegro:

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

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

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803) for

devices or postmarketing safety reporting (21 CFR 4, Subpart B) for combination products (see https://www.fda.gov/CombinationProducts/GuidanceRegulatoryInformation/ucm597488.htm); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/) and CDRH Learn (http://www.fda.gov/Training/CDRHLearn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (http://www.fda.gov/DICE) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

Matthew Krueger, M.S.E.
Assistant Director
THT5A1: Neurosurgical Devices
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Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: 06/30/2020
See PRA Statement below.

510(k) Number *(if known)*
K190246

Device Name
NeuroShield [TM]

Indications for Use *(Describe)*

Under supervision of a healthcare professional
• NeuroShield[TM] is indicated for the repair of peripheral nerve injuries in which there is no gap or where a gap closure can be achieved by flexion of the extremity.

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

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

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Section 5 - 510(k) Summary

A. Submitted by: **Monarch Bioimplants GmbH**
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B. Date Prepared: Apr/23/2019

C. Contact Person: Dr. Rivelino Montenegro
CEO
Phone: +41(0)41 4552261

D. Product Name: NeuroShield™

E. Common Name: Nerve Cuff

F. Classification number/name: 882.5275/Nerve Cuff

G. Product Code: JXI

H. Device description:

NeuroShield™ is a chitosan membrane to provide a non-constricting protection for peripheral nerves. NeuroShield™ is designed to be an interface between the nerve and the surrounding tissue for uses to treat nerve injuries. When hydrated, NeuroShield™ is easy to handle, soft, pliable, nonfriable, porous and transparent.
NeuroShield™ is provided as a sterile, non-pyrogenic rectangular sheet in the size of 40 x 30 x 0.03 mm and is intended for single use.
NeuroShield™ is perforated to support the transport of physiological liquid through the wall of the device thereby easing the attachment to nerve tissue. With a diameter of 0.2 mm the holes make up 0.8% of the surface area of NeuroShield™.
NeuroShield™ can easily be placed over the injured nerve, and can be sutured if necessary. Furthermore, the device can be trimmed or shaped to the appropriate size to fit the nerve tissue to be treated.
The picture below shows a sketch of NeuroShield™.

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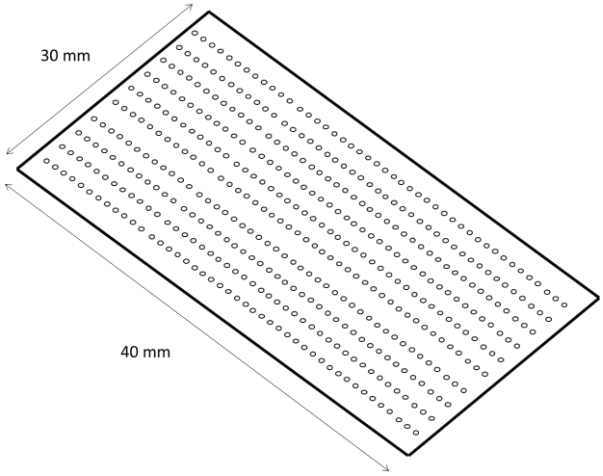

Picture 1. Sketch of NeuroShield™. A chitosan membrane of 30 x 40 x 0.03 mm with microscopic porosity.

I. Indications for Use:

Under supervision of a healthcare professional

- NeuroShield™ is indicated for the repair of peripheral nerve injuries in which there is no gap or where a gap closure can be achieved by flexion of the extremity.

J. Predicate Device:

NeuroShield™ is substantially equivalent in function and intended use to:

510(k) number	Device name	Device company
K103081	Cova™ORTHO-NERVE	Biom'Up Advance Biomaterials
K143711	Reaxon® Plus	Medovent GmbH
K152967	Nerbridge™	Toyoba Co., Ltd.

The predicate devices are described in more detail below:

- Cova™ORTHO-NERVE is a pure collagen membrane designed to be used as a barrier to allow guided healing along distinct anatomical planes. It is completely resorbable within a time frame that is compatible with healing. The membrane is obtained by standardized, controlled manufacturing processes. Cova™ORTHO-NERVE is further sterilized in double-pouches by gamma-irradiation.
  Cova™ORTHO-NERVE membranes are designed to be resorbable, non inflammatory and biocompatible for uses to treat peripheral nerve injuries. When wetted, the membrane is conformable, elastic and easy to handle. It can be used alone or, if

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needed, it can be sutured in place. Cova™ORTHO-NERVE is provided in rectangular sheets of 15 x 25 mm, 20 x 30 mm, 30 x 40 mm and 40 x 60 mm. Furthermore, the device can be easily trimmed or shaped to the appropriate size, without tearing or fragmenting, to fit the zone to be treated.

- Reaxon® Plus is a flexible and transparent chitosan based implant designed for repair of peripheral nerve discontinuities up to 10 mm and where gap closure can be achieved by flexion of the extremity.
  Reaxon® Plus was developed to provide a protective environment for axonal growth across a nerve gap. When hydrated, Reaxon® Plus is an easy to handle, soft, pliable, transparent chitosan tube. Reaxon® Plus is provided sterile, non-pyrogenic, for single use in double blister packages in a variety of sizes.

- Nerbridge™ is a product composed of polyglycolic acid and collagen derived from porcine skin. Nerbridge™ is a flexible, resorbable and semipermeable tubular membrane matrix filled with porous collagen that provides a non-constricting encasement for injured peripheral nerves for protection of the neural environment. Nerbridge™ is designed to be an interface between the nerve and the surrounding tissue. When hydrated, Nerbridge™ is a pliable, soft, non-friable, porous conduit.
  The resilience of Nerbridge™ allows the product to recover and maintain closure without constricting the nerve once the device is placed around the nerve.
  Nerbridge™ is manufactured using validated viral inactivation and removal processes for the collagen. The product is provided in a foil pouch, sterile, nonpyrogenic, for single use only, in a variety of sizes, and placed in an outer Tyvek header bag for added protection.

A table of comparative features may be found below.

Parameter	Device	Predicate Device	Predicate Device	Predicate Device
Device name	NeuroShield™	Cova™ ORTHO-NERVE	Reaxon® Plus	Nerbridge™
Company Name	Monarch Bioimplants GmbH	Biom'Up Advance Biomaterials	Medovent GmbH	Toyoba Co., Ltd.
510(k) #		K103081	K143711	K152967
Material	Chitosan	Collagen	Chitosan	Collagen and Polyglycolic Acid

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Section 5 - 510(k) Summary

Indications For Use	Indicated for the repair of peripheral nerve injuries in which there is no gap or where a gap closure can be achieved by flexion of the extremity.	Indicated for the repair of peripheral nerve injuries in which there is no gap or where a gap closure can be achieved by flexion of the extremity.	Reaxon® Plus is indicated for repair of peri-pheral nerve discontinuities up to 10 mm and where gap closure can be achieved by flexion of the extremity.	Indicated for the repair of peripheral nerve injuries in which there is no gap or where a gap closure can be achieved by flexion of the extremity.
Packaging	Double pouch	Double blister	Double blister	Foil double pouch within protective outer pouch
Physical structure	Membrane, rollable if needed	Membrane, rollable if needed	Tube	Cylindrical
Sterilization Method	EO	Gamma irradiation	EO	EO

In *vitro* and in *vivo* biocompatibility testing according to ISO 10993 standards and bench tests, have been performed on NeuroShield™. These tests proved that NeuroShield™ is as safe as, and performs as well as its legally marketed predicate devices Cova™ORTHO-NERVE, Reaxon® Plus and Nerbridge™.
Below there is a summary of each study that was performed.

Cytotoxicity
Purpose: To evaluate *in vitro* the cytotoxicity potential of NeuroShield™.
Method: A single preparation of the test article was extracted in single strength Eagle Minimum Essential Medium (EMEM 10) at 37 ± 1°C for 72 hours. This article was placed on triplicate sub-confluent monolayers of L-929 mouse fibroblast cells. Separate monolayers were prepared for triplicate negative and positive controls. After incubating at 37 ± 1°C in 5 ± 1% $C0_2$ for 48 ± 2 hours, the cultures were stained with a trypan blue solution. The cultures were then examined microscopically to determine cell morphology.
Result: Only slight evidence of cell lysis or toxicity (grade 1). The test article extract met the requirements of the test since the grade was less than a grade 2 (mild reactivity).

Acute systemic toxicity
Purpose: To evaluate for acute systemic toxicity in mice.
Method: A single dose of the appropriate test article extract was injected into a group of five mice. Similarly, a separate group of five mice was dosed with each corresponding

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extraction vehicle alone (control blank). The mice were observed for signs of systemic toxicity immediately after injection and at 4, 24, 48 and 72 hours after injection. Body weights were recorded prior to dosing and at 24, 48 and 72 hours after injection.
Result: There was no mortality or evidence of systemic toxicity from the extracts injected into mice. Each test article extract met the requirements of the study.

Sensitization
Purpose: to evaluate the potential of the test article to cause delayed dermal contact sensitization in the guinea pig maximization test.
Method: The test article was extracted in 0.9% sodium chloride (SC) and sesame oil (SO). Each extract was intradermally injected (induction I) and topically applied (induction II) to ten test guinea pigs (per extract) in an attempt to induce delayed sensitization. The extraction was similarly injected and topically applied to five control blank guinea pigs (per vehicle). Following recovery period, the test and control blank animals received a challenge patch of the appropriate test article extract and the extraction vehicle. All sites were scored at 24 (± 2) and 48 (± 2) hours after patch removal.
Result: The test article extracts showed no evidence of causing delayed dermal contact sensitization in the guinea pig. The test article was not considered a sensitizer in the guinea pig maximization test.

Irritation/Intracutaneous reactivity
Purpose: To evaluate for the potential to cause irritation following intracutaneous injection in rabbits.
Method: The test article was extracted in 0.9% sodium chloride (SC) and sesame oil (SO). A 0.2 mL dose of the appropriate test article extract was injected intracutaneously into five separate sites on the right side of the back of each of three rabbits. Similarly, the extract vehicle alone (control blank) was injected on the right side of the back of each rabbit. The injection sites were observed immediately after injection. Observations for erythema and edema were conducted at 24, 48, and 72 hours after injection.
Result: Under the conditions of the study, the test article met the requirements of the test since the difference between each test extract overall mean score and corresponding control blank overall mean score was lower than 1.0 (0.0 and 0.3 for the SC and SO test extracts.

Systemic toxicity
Purpose: To evaluate for the potential to cause systemic toxicity.
Method: Twelve male and 12 female rats were randomly assigned to either the test or negative control group (6/sex/group). Rats were observed daily for overt signs of toxicity. Detailed clinical examinations were conducted weekly. Rats were weighed prior to implantation, at weekly intervals, the day prior to termination and on the day of euthanasia. After 4 weeks, blood samples were collected for hematology and clinical chemistry analysis and the rats were euthanized. A necropsy was conducted, selected

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organs were collected and weighed. A microscopic evaluation of the collected organs was conducted.
Result: Under the conditions of this study, there was no evidence of systemic toxicity from the test article following subcutaneous implantation of NeuroShield™ in the rat.

Implantation
Purpose: To evaluate the local tissue response of the test article implanted in muscle tissue of the rabbit.
Method: The test article and negative control were intramuscularly implanted and animals were euthanized 12 weeks later. Muscle tissues were excised and the implant sites examined macroscopically. A microscopic evaluation of representative implant sites from each animal was conducted to further define any tissue response.
Result: The macroscopic reaction was not significant as compared to the negative control article. Microscopically, the test article was classified as a moderate irritant as compared to the negative control article.

Pyrogenicity (USP)
Purpose: To evaluate for the potential to induce a pyrogenic response following intravenous injection in rabbits based on the United States Pharmacopeia (USP 39 – NF 34).
Method: The test article was extracted in 0.9% sodium chloride (SC). A 10 mL/kg dose of the appropriate test article was intravenously injected to 3 rabbits. Rectal temperature was measured every 30 minutes for 3 hours after injection.
Result: Non-pyrogenic. Under the conditions of the study, the test article met requirements of the USP 39 - NF 34. The test article was judged as non-pyrogenic.

Genotoxicity
Purpose: To evaluate for the potential to induce reverse mutations at the histidine locus of the *Salmonella typhimurium* tester strains TA98, TA100, TA1535 and TA1537 or at the tryptophan locus of *Escherichia coli* tester strain WP2uvrA in a bacterial reverse mutation assay.
Method: The test article was extracted in 0.9% sodium chloride (SC) and in dimethyl sulfoxide (DMSO). The assay was conducted in the presence and absence of metabolic activation.
A preliminary dose range finding (DRF) assay was firstly conducted on 5 doses of the SC and DMSO test article extract (100%, 50%, 25%, 12.5% and 6.25%, v/v), on the *Salmonella typhimurium* LT2 TA100 tester strain and *Escherichia coli* tester strain WP2uvrA in the absence and presence of metabolic activation using the direct incorporation method to find the suitable nontoxic dose of the extracts to be tested in mutagenicity assay. For both SC and DMSO extracts, the highest nontoxic dose was

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found to be 100 µL/plate of the 100% (v/v) extract, both in the absence and presence of metabolic activation.
Tubes containing molten top agar were inoculated with culture from one of the five tester strains, along with the test article extracts tested at the single dose of 100 µL/plate of the 100% extract. An aliquot of phosphate buffer or rat liver S9 Mixture providing metabolic activation was added. The mixture was poured across triplicate plates. Parallel testing was conducted with control blank and positive controls. The mean number of revertants for the test extract plates was compared to the mean number of revertants of the appropriate control blank plates for each of the five tester strains.
Result: Non-mutagenic. The SC and DMSO test article extract were considered to be non-mutagenic to *S. typhimurium* tester strains TA98, TA100, TA1535, and TA1537, and to *E. coli* WP2uvrA tester strain.

Hemolysis
Purpose: To evaluate the hemolytic properties of the material.
Method: Blood was obtained from human, pooled, diluted, and added to triplicate tubes with the calcium and magnesium-free Dulbecco's phosphate buffered saline (CMF-DPBS) test article extract. These combinations were evaluated to determine whther extract of the test article would cause in vitro red blood cell hemolysis. Control blanks, negative control and positive controls were prepared in the same manner as the test article. The tubes were then maintained for at least 3 hours at 37 ± 2°C with gentle periodic inversions at approximately 30 minutes intervals. Following incubation, suspensions were mixed gently and centrifuged. The resulting supernatant was added to Drabkin's reagent. The absorbances of the solutions were spectrophotometrically measured at the wavelength of 540 nm.
Result: Under the conditions of this study, the mean hemolytic index for the test article extract was of 0.0%. The test article extract was non hemolytic.

Based on the results presented above we conclude that NeuroShield™ is as safe as its predicate devices for its intended use.

Performance Characteristics

The mechanical and physical characteristics (bench tests) of NeuroShield™ were evaluated in a series of tests. These tests were conducted to ensure that NeuroShield™ possess the mechanical and physical properties that determine its suitability for use in the human body. Testing has demonstrated that the nerve cuff is able to hold a suture and to be placed around surfaces.
These tests were done in direct comparison to the NeuroShield™ predicate devices Cova™ORTHO-NERVE and Reaxon® Plus.

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Section 5 - 510(k) Summary

Dimensional (visual inspection) and odor testing

Purpose: To verify that the dimensions of NeuroShield™ were within specified tolerances as indicated in the packaging in comparison to the predicate devices. The color and odor were also registered.

Method: Direct measurement of the dimensions of the membranes as well direct comparison to the predicate devices.

Result: Dimensional analysis was completed to verify that the dimensions of NeuroShield™, color and odor were within specified tolerances of the indicated values and in comparison to the predicate devices.

Feel test after wetting

Purpose: The purpose of the feel test is to observe whether the product is soft and stable enough in the hands of a surgeon, who has to handle, fold or trim the device before implanting it.

Methods: After wetting in PBS for 10 minutes the samples are handled as a surgeon would do in a real case before implanting. It is important to observe if the device is soft and pliable (to be folded, rolled, etc.) and whether it can be handled and clamped with tweezers without breaking in pieces (nonfriable).

Result: The feel test (handling) showed that NeuroShield™ is as soft, pliable and nonfriable as the predicate devices Cova™ORTHO-NERVE and Reaxon® Plus.

Pliability around round surface

Purpose: The purpose of this test is to check the ability of the device to wrap around round surfaces such as nerves.

Method: After wetting in PBS for 10 minutes the samples are placed around rods of different diameters.

Result: NeuroShield™ is as pliable as its predicate devices Cova™ORTHO-NERVE and Reaxon® Plus to wrap around round surfaces as for example nerve cables.

Swelling and water uptake

Purpose: To check how fast the swelling takes places and the change in dimensions. This is important since NeuroShield™ and its predicate devices Cova™ORTHO-NERVE and Reaxon® Plus are hydrogels and require aqueous environment to become completely soft and of ease handling. The recommended time in contact with saline solution before implantation is 10 minutes, therefore this test checks whether the swelling and water update is almost complete in the first 10 minutes of contact with aqueous solution.

Method: The devices were placed in PBS (pH 7.4) at room temperature, while the length and width (or inner diameter) were measured in different time intervals. The samples were also weighed (g) at the respective time intervals (10 minutes, 2, 3 and 24 hours).

Result: NeuroShield™ needs only 10 minutes in contact with aqueous solution to be fully hydrated, similarly to its predicate devices.

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Section 5 - 510(k) Summary

Suture retention strength test

Purpose: The purpose of the retention strength test was to verify that NeuroShield™ has sufficient strength to resist suture pull-out under loads exceeding the ones anticipated in the intended use environment.

Method: After 24 hours in PBS (pH 7.4) at room temperature, the devices were incubated for 1 hour at 37°C for the measurement of suture retention.

For this measurement, the devices had one extremity clamped at the lower clamp of a mechanical tester.

A suture thread (USP 6/0 Prolene) was used to pierce the devices (NeuroShield™ and Cova™ORTHO-NERVE were folded for the needle to pierce through two walls, while Reaxon® Plus was pierced twice across the diameter of the tube) at 2 mm from the top extremity and the suture was clamped at the top clamp of the mechanical tester.

The force required to pull out the thread at constant cross-head speed of 1 mm/min was monitored.

Result: Suture retention strength testing was completed to verify that NeuroShield™ has sufficient strength to resist suture pull-out under loads exceeding those anticipated in the intended use environment.

In *vivo* performance testing

Purpose: The aim of this project was to conduct an in vivo study in a standardized rat preclinical model to demonstrate that a novel chitosan device (Neuroshield) has similar biocompatibility and performance properties in the peripheral nerve repair as the chitosan device Reaxon® Plus.

Methods: The functional animal study was performed with 17 adult female Wistar rats, weighing approximately 200 g. Median nerves were repaired with Reaxon® Plus and NeuroShield and harvested at 2, 6 and 12 weeks. The animals were divided in the following experimental groups:

1) Nerves repaired with Reaxon® Plus for 2 weeks (n=3);
2) Nerves repaired with Neuroshield for 2 weeks (n=4).
3) Nerves repaired with Reaxon® Plus for 6 weeks (n=3);
4) Nerves repaired with Neuroshield for 6 weeks (n=3);
5) Nerves repaired with Reaxon® Plus for12 weeks (n=4);
6) Nerves repaired with Neuroshield for 12 weeks (n=4).

Functional analysis was performed on rats at 2, 6 and 12 weeks using the grasping test in order to evaluate the functional recovery of finger flexor muscles after median nerve reconstruction.

The regenerated nerve samples were harvested 2, 6 and 12 weeks after the surgery and morphological analyses by light and confocal microscopy, as well as electron microscopy, were carried out in order to evaluate the nerve regeneration, including the number of myelinated fibers, axon and fiber diameter, myelin thickness and g-ratio. In addition, the tissue reaction was investigated by evaluating the presence of multinucleated giant cells and activated ED1-immunopositive macrophages, as well as polymorphonuclear cells,

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lymphocytes, plasma cells, necrosis, neovascularization, and fibrosis of the tissue at and surrounding the treatment site.
Degradation was assessed based on the amount of absorbable material left at the implant site, as well as material parameters, such as fragmentation and/or debris presence, form and location of remnants of degraded material, and by a histological assessment of the tissue at and surrounding the treatment site.
Result: Behavioral analysis on rats of both experimental groups evaluated after median nerve repair demonstrated that Neuroshield allowed neuromuscular functional recovery equivalent to Reaxon® Plus. Immunohistochemical and electron microscopical analyses carried out inside the two conduits showed that few axons, together with glial cells are already present after two weeks in both conduits; at 6 and 12 weeks the conduits are both colonized by regenerating fibers and Schwann cells. Morphoquantitative stereological analysis showed no statistical differences between the two experimental groups. Additionally, a similar tissue response was observed for both devices. Moreover, no statistical differences were found as regards the number of ED1-immunopositive macrophages in Neuroshield at 6 and 12 weeks, confirming steady state conditions. In conclusion, altogether the results revealed a substantial equivalence between the two devices in repairing a 10 mm-long nerve gap of the rat median nerve.
Beginning fragmentation of NeuroShield was observed at 12 weeks post-implantation, and fragments were detected within the regenerating tissue and in the surrounding connective tissue.
The thickness of the membrane has decreased significantly compared to the 2 weeks animals, which is in consistency with the significant mass loss observed in the in vitro testing as result of enzymatic degradation. Regenerated fibers and blood vessels occurred according to the time and progress of the regeneration process. There were no signs of fibrosis or scar tissue being formed around the degrading material.

K. Conclusion:

NeuroShield™ is intended for use in repair of peripheral nerve discontinuities and where gap closure can be achieved by flexion of the extremity.
Based on the results of animal studies, in *vitro* product characterization studies, in *vitro* and in *vivo* biocompatibility and performance studies, we conclude that NeuroShield™ is as safe as, and substantially equivalent to its predicate devices.