Siemens Healthineers
Business Area Ultrasound

CW2 Biological Evaluation Report

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CONTENT

1. Summary

A biological risk assessment of CW2 has been performed. A biological risk assessment identifies areas of concern to be addressed by literature review, clinical experience, and testing. The evaluation of the biological safety of a medical device is a strategy planned on a case-by-case basis to identify hazards and estimate the risks of known hazards. Testing strategies and or justifications for waiving biocompatibility testing is developed using clear, concise, logical, and scientifically reasoned plans for evaluating biological safety that demonstrate that all biological hazards have been considered and relevant risks assessed and controlled.

To evaluate the biological safety of the device, the following factors were considered: type of patient contact; potential hazards associated with the materials of construction, the history of clinical use and testing of the materials of construction, and the results of biocompatibility testing performed on the representative device; and other information available in the literature. Based upon examination of this information, use of the CW2 transducer would not be expected to result in an adverse biological response in patients. This risk assessment indicates that the likelihood of a toxic effect from these devices is negligible and that the devices can be considered safe for use as intended. No further biocompatibility or chemical testing is recommended.

CW2 meets the requirements of ISO 10993-1:2018, EN ISO 14971:2020, FDA General Guidance on the Use of International Standard ISO 10993-1:2020, and the European Union Medical Device Regulation 2017/745/EU for a surface medical device that has limited (≤ 24 hours) contact with skin and can be considered safe for use as indicated.

2. Signature Page

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3. Introduction

3.1. Background Information

CW2 is continuous wave transducer, intended for Adult Echocardiography, Pediatric Echocardiography. This transducer is manufactured and packaged at the Sound Technology as OEM supplier. Biocompatibility testing was conducted to assess biological safety per ISO 10993-1:2018 and testing is evaluated in this document.

3.2. Purpose

The purpose of this report is to determine the overall biological safety of CW2 transducer using results of biocompatibility testing, the type of patient contact, the materials of construction and the history of clinical use. This biological risk assessment focuses only on CW2, listed below in Table 1 and does not address the biological risks associated with other sets, devices or accessories:

Table 1: Transducers Identification

Product Name	**Part Number**	**Maximum Patient Contact Surface area, cm^2**
CW2	10789380	7.95

3.3. Responsibilities

Siemens Medical Solutions, USA Inc. provided product information and test results. The biological risk assessment was performed under the responsibility of Irwin & Associates and reviewed by Siemens Medical Solutions USA and SIEMENS Healthineers Ltd South Korea.

3.4. Risk Assessment Guidelines

The biological risk assessment is a comprehensive document, evaluating the biocompatibility of CW2 against current European/ FDA requirements. Accordingly, this document focuses on the requirements and/or recommendations listed in Table 2.

Table 2. Applicable Documents

Reference	**Title**
EU MDD	Applicable sections of European Union Medical Device Directive 93/42/EEC amended 2007/47/EC
EU MDR	Applicable sections of the European Medical Device Regulation 2017/745/EU (published in Official Journal of the European Union on May 5th, 2017)
2016 FDA Biocompatibility Guidance	Use of International Standard ISO 10993-1, "*Biological Evaluation of Medical Devices Part 1: Evaluation and testing within a risk management process*", Guidance for Industry and Food and Drug Administration Staff, June 2016
2020 FDA Biocompatibility Guidance	Use of International Standard ISO 10993-1, "*Biological Evaluation of Medical Devices Part 1: Evaluation and testing within a risk management process*", Guidance for Industry and Food and Drug Administration Staff, Sep 04 2020
ISO 10993-1:2018	Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process
ISO 10993-2:2006	Biological Evaluation of Medical devices – Part 2: Animal welfare requirements
ISO 10993-5:2009	Biological Evaluation of Medical devices – Part 5: Tests for *in vitro* cytotoxicity

Reference	Title
ISO 10993-10:2010	Biological Evaluation of Medical devices – Part 10: Tests for irritation and skin sensitization
ISO 10993-12:2012	Biological Evaluation of Medical devices – Part 12: Sample preparation and reference materials
ISO 14971:2007 EN ISO 14971:2012	Medical Devices – Application of risk management to medical devices, Annex I: Guidance on Risk Analysis Procedures for Biological Hazards
ISO 14971:2019 EN ISO 14971:2020	Medical Devices – Application of risk management to medical devices, Annex I: Guidance on Risk Analysis Procedures for Biological Hazards
21 CFR, Part 58	USA, Good Laboratory Practice reference in the Code of Federal Regulation (CFR)

Note: Standards referred to in this document are listed in this section. Otherwise, the complete reference (including date and title) will be indicated.

4. Device Description

CW2 is re-usable and non-sterile type transducer. It is intended for Adult Echocardiography, Pediatric Echocardiography as continuous wave transducer.

See the Figure 1 for general reference of the transducer structure. The target markets for this transducer is worldwide, including USA, EU, and Asia. Refer to Tables 3 to 5 for the materials, manufacturing process and manufacturing aids used.

[CW2]

Figure 1. Transducer structure of CW2

Table 3: Patient-Contacting Materials of Construction for CW2

Transducer Section	Base Material(s)	Patient Contact
Acoustic Lens	Polyphenylene Oxide, Ultem 1000	Skin
Adhesive	Epoxy, Loctite 380 Black Max Metacast 401	Skin

Transducer Section	Base Material(s)	Patient Contact
Housing	Polyphenylene Oxide, Ultem 1000	Skin

Table 4: CW2 Colorants

Transducer Section	Colorant(s)	Colorant Composition
Acoustic Lens	Black	Proprietary
Adhesive	Black	Proprietary
Housing	Black	Proprietary

5. Device Manufacturing Process

Table 5: Manufacturing/Cleaning Aids Used

Description	Process	Potential Contact
Cleaning (Debris Removal)	Isopropanol/Acetone	Skin
Hi-Pot Testing	Saline	Skin

The manufacturing solvents listed in the table above are of relatively low risk and toxicity. The saline solution will likely evaporate during manufacturing process. Any residue left will not have a toxicity impact since the saline solution is USP grade which is certified to not have toxicity impact in skin contact surfaces. The IPA is used to remove debris off the surface of the device during manufacturing process. The IPA is a volatile solvent and will likely flash off during the manufacturing process.

A flow chart of manufacturing processes for CW2 is provided in Appendix 2. Certificates of analyses and material data sheets are provided in Appendix 3.

6. Device Categorization

When used as intended, CW2 is categorized according to ISO 10993-1 as surface medical devices that have limited (≤ 24 hours) contact with skin.

Because of CW2 categorization, consideration must be given to all relevant endpoints defined by ISO 10993-1:2018 and FDA General Guidance: 2020- Biological Evaluation of Medical Devices Part 1, (see Table 6).

Table 6. Biological Endpoints to be Considered for CW2

Biological Endpoint	Applicable ISO 10993 Standard
Cytotoxicity	ISO 10993-5: Tests for Cytotoxicity – *In Vitro* methods
Sensitization	ISO 10993-10: Tests for Sensitization and Irritation
Irritation (Intracutaneous)	ISO 10993-10: Tests for Sensitization and Irritation

While all of the endpoints for Cytotoxicity, Sensitization and Irritation listed above must be considered, they can be addressed in a number of different ways including biocompatibility testing and/or written justification/risk assessment, if relevant information is available as stated in the introduction section of ISO 10993-1:2018.

7. Method

7.1. Safety Assessment Approach Used

This document assesses the risk posed to patients for whom CW2 is used.

EN ISO 14971:2020, Medical devices – *Application of risk management to medical devices* states that toxicological risk assessment shall be based on:

- □ The physical and chemical characteristics of the device components and materials.
- □ Any history of clinical use or human exposure data.
- □ Any existing toxicology and other biological safety data on the product components and materials.
- □ Test procedures and results.

As stipulated in Annex I of ISO/EN ISO 14971 related to the guidance on risk analysis process for biological hazards:

- □ Clause I.2.1: *The amount of data required and the depth of the investigation will vary with the intended use and are dependent upon the nature and duration of patient contact. […]. Current knowledge of the material/medical device provided by scientific literature, previous clinical experience, and other relevant data should be reviewed to establish any need for additional data*".
- □ Clause I.2.4: "*ISO 10993-1 gives guidance on which tests in the ISO 10993 series should be considered for a particular application. The need for testing should be reviewed on a case-by-case basis in the light of existing data, so that unnecessary testing is avoided*". The risk assessment process consists of:
  1) Risk Analysis
  2) Risk Evaluation
  3) Risk Control
  4) Overall Risk Evaluation
  5) Consideration of Production and Post-Production Information

Collectively, knowledge of the composition of a medical device, including additives and processing aids, prior use of the relevant material(s) in a predicate device or similar device, and biological safety tests should provide predictive evidence of potential hazards to users of the device under consideration.

Evaluation of the chemical nature of the material can take the form of experimental data and/or information on the chemistry of the materials/components involved. Literature studies conducted on the materials help evaluate the biological response and are useful in assessing a finished medical device for its intended use/intended purpose. Some factors that affect the biocompatibility of the material include the identity, concentration, availability, and toxicity of all constituents such as additives, processing aids, and monomers.

To evaluate prior use, information on previous uses of the device/materials or intended additives, and any adverse

reactions encountered, should be reviewed. Account should be taken of the intended use, the concentration of the ingredients, and current toxicological information. Biological safety should be considered giving special attention to the ISO 10993 series for a particular application. The need for testing should be reviewed on a case-by-case basis.

The amount of data required on a material, and the depth of the investigation, is dependent upon the intended use in manufacturing of devices and the function and duration of patient contact. Knowledge of a material's composition and potential leachable compounds, combined with results from biological safety testing, should provide predictive evidence of any potential toxicological risk to patients.

Devices must be designed and manufactured in such a way as to reduce to a minimum the risks posed by substances leaching from the product. Special attention shall be given to substances that are Carcinogenic, Mutagenic or Reprotoxic (CMR substances) according to European Regulations and/or international Agencies. [2, 3, 4, 5]

International Standards Organization 10993-1:2018: Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process includes the recommended biological testing and the principles governing the biological evaluation of medical devices. ISO 10993-1:2018 applies to the non-clinical or pre-clinical testing of devices. It should be noted that clause 4.5 states:

> "*All known possible biological hazards shall be taken into account for every material and final product, but this does not imply that testing for all possible hazards will be necessary or practical*."
>
> Clause 4.1 of this standard specifies:
>
> > "*Evaluation can include both a review of relevant existing preclinical and clinical data and actual testing. Such an evaluation might result in the conclusion that no testing is needed if the material has a demonstrable safe history of use in a specified role and physical form that is equivalent to that of the device under design*."
>
> ISO 10993-1 contains many other clauses that allow for exceptions and exemptions from pre-clinical biological testing. Notable examples are:
>
> Clause 6.3.1.b: *The choice of test procedures shall take into account*:
>
> Clause 6.3.1.b.4: *certain biological tests…are not justifiable where the presence of leachable chemicals has been excluded, or where chemicals have a known and acceptable toxicity profile*; Clause 6.3.1.b.6: *the existing information based on the literature, previous experience, and non-clinical tests*;
>
> Clause 6.3.1.b.8: *the protection of humans is the primary goal of this part of ISO 10993; a secondary goal is to ensure that any pain, suffering, distress or lasting harm to the animals used shall be minimized*.

The introduction to ISO 10993-1:2018 states: *It is not intended that ISO 10993 provide a rigid set of test methods, including pass/fail criteria, as this might result in either an unnecessary constraint on the development and use of novel medical devices, or a false sense of security in the general use of medical devices. Where a particular application warrants it, experts in the product or in the area of application concerned can choose to establish specific tests and criteria, described in a product-specific vertical standard*.

This part of ISO 10993 is intended for use by professionals, appropriately qualified by training and experience, who are able to interpret its requirements and judge the outcome of the evaluation for each medical device, taking into consideration all the factors relevant to the medical device, its intended use and the current knowledge of the medical device provided by review of the scientific literature and previous ` experience.

Annex A states: *Table A.1 is a framework for the development of a biocompatibility evaluation and is not a checklist (see Clause 6). For particular medical devices, there is a possibility that it will be appropriate to include additional or fewer endpoints than indicated in Table A.1*.

7.2. Biological Risk Estimation

Identification of the materials and processes used in the manufacture of a medical device enables the intrinsic

toxicity of the device to be investigated. The biological risks arising from the use of medical devices are related to two main sources, regardless of the type and duration of body contact:

Raw materials used to fabricate the medical device, which can combine different chemicals capable of leaching from the device and/or producing degradation products that cause adverse effects once in contact with tissues and body fluids. Moreover, the surface state, porosity, geometry, aspect (solid, gel, liquid) may also influence the biological reaction in the immediate vicinity of the medical device (tissues, bone, blood), i.e., its local tolerance, hemocompatibility.

Manufacturing process, including machining, assembly, cleaning, packaging and sterilization, are all steps that can provide residues which may be bioavailable once in contact with the body and body fluids and can be responsible for additional biological hazards.

7.3. Literature Search

In order to identify relevant toxicity data on specific materials, multiple sources were searched for data. These sources included on-line databases such as: ToxPlanet (which indexes dozens of relevant toxicity databases such as RTECS, FDA's Select Committee on GRAS Substances (SCOGS) Reports database, European Chemicals Agency database, ATSDR reports database), ChemIDplus (which indexes databases such as HSDB, DART, EMIC, CCRIS, IRIS, Medline, and Toxline), TSCATS (which catalogs toxicity studies submitted to the EPA under TSCA), ChemFinder, and the World Wide Web using appropriate search engines. The search terms included elements such as CAS numbers (when available), chemical names, safety, chemistry, toxicology, toxicity or biocompatibility. Please refer to the result of the literature search from the appendix 1, Risk Analysis of Device Material.

8. Results

8.1. Risk Analysis of Device Materials

After an analysis of the materials used to construct the CW2 transducer, it was apparent that the materials used are well characterized with a long history of clinical use in similar or closely related, approved and marketed medical devices. A detailed summary of the risk analysis performed on the device materials of construction is presented in Appendix 1.

8.2. Risk Analysis of Manufacturing Processes

After an analysis of the manufacturing processes used to construct CW2, the materials of manufacturing used in this process were judged to be appropriate and represent those commonly used within the medical device industry. The processing and cleaning procedures presented were also judged to be appropriate and to represent those commonly used in the medical device industry. The manufacturing solvent with potential patient contact, IPA has relatively low toxicity, as well as being volatile and evaporating quickly during manufacturing processes, leaving no residues behind.

8.3. Biological Endpoints Evaluated

A detailed summary of the biocompatibility testing conducted on CW2 is presented in Appendix 4. A high-level summary of this testing is shown in Table 7. All testing was done on the full patient-contacting portion of the transducer.

Table 7. Summary of Biocompatibility Testing Conducted

Current ISO Standard	ISO Standard Used in Testing	Test	Results	Study #
10993-5:2009	10993-5:2009	Cytotoxicity Study, ISO Elution Method	Non-cytotoxic	15T 48244 03
10993-10:2010	10993-10:2002	Sensitization Test	Non-sensitizer	09T 31764 01 09T 31764 02

10993-10:2010	10993-10:2002	Intracutaneous Irritation Study in Rabbits	Non-irritant	09T 32454 01 09T 32454 02

8.4. Gap Analysis of the Endpoints Evaluated

Although the tests were conducted on prior ISO 10993 standards. The protocol and test methods were compared and the test data remains valid to support the biocompatibility of the current standards were used in the biocompatibility testing of the CW2 transducer.

Appendix 4 provides a detail summary of the test methods used and provides the Gap Analysis. A Gap Analysis is provided below:

8.4.1 Cytotoxicity Study

ISO -10993-5, test for In-vitro Cytotoxicity, originated in 1993, was revised in 1999,2006, 2010, and revised again in 2016. The changes in 10993-5 from 1993 to the current 2016 version included changes to the existing annexes, the addition of new informative annexes. The review of the test reports and test methods did not identify any gaps from the current standard. Additional testing is not needed

8.4.2 Intracutaneous (Irritation) and Sensitization

ISO 10993-10, Tests for Irritation and Sensitization, originated in 1993, was revised in 2002, 2010 and reconfirmed again in 2016. The changes in 10993-10 from 2002 to the current 2010 version included changes to the existing annexes, the addition of new informative annexes, and addition of special irritation tests in annex B. None of these changes affected the Intracutaneous and Sensitization tests as performed on the CW2 transducers. The review of the test reports and test methods did not identify any gaps from the current standard. Additional testing is not needed.

9. Risk Assessment Discussion

9.1. Biological Endpoints Evaluated

A summary of the methods used to address each relevant biological endpoint appears in Table 9.

Table 9. Methods of Evaluation

Biological Endpoint	Testing (Method Recommended or Performed)
Cytotoxicity	Testing performed
Sensitization	Testing performed
Intracutaneous Reactivity/Irritation	Testing performed

9.2. Clinical Data and Post Market Surveillance Data

The worldwide clinical history of this transducer from 2014 – 2020 consists of the following:

- No complaints related to irritation
- No complaints related to allergic reactions

None of the complaints reviewed are related to biological reactions consistent with biocompatibility failures. With no findings on record, the occurrence of harm related to biocompatibility is improbable for this time period.

10. Risk Assessment and risk Control

Based upon the risk analysis, use of the CW2 would not be expected to result in an adverse biological response in patients. This risk assessment indicates that the likelihood of a toxic effect from CW2 is negligible and that the device can be considered safe for use as intended.

Consideration has been given to all potential biological hazards for the materials and final product and testing for each hazard is not necessary.

11. Reassessment of Risk

This risk assessment is valid for the current iterations of the CW2 listed in Section 3.2 above. It applies to devices manufactured using the current processes and techniques. As specified in Clause 4.9 of ISO 10993-1, “The biological risk assessment of materials or final products shall be re-evaluated if any of the following occur”:

a) any change in the source or in the specification of the materials used in the manufacture of the product.

b) any change in the formation, processing, primary packaging or sterilization of the product.

c) any change in the manufacturer’s instructions or expectations concerning storage, e.g. changes in shelf life and/or transport.

d) any change in the intended use of the product; any evidence that the product can produce adverse biological effects when used in humans.

Systematic approach for biologic evaluation of the medical device as indicated in EN ISO 10993-1 as part of a risk management process can be checked from the Appendix 5 - Systematic approach for biological evaluation of the medical device.

12. Conclusion

This biological risk assessment was supported by information on the CW2 transducer. Materials of construction, available toxicological data on these materials, and biological data on the CW2 transducer as well as the clinical safe history of use data on this currently marketed device. This risk assessment indicates that the likelihood of a toxic effect from the CW2 transducer is low. No further testing is recommended.

CW2 transducer meets the requirements of ISO 10993-1:2018, EN ISO 14971:2020, FDA General Guidance on the Use of International Standard ISO 10993-1:2020, and the European Union Medical Device Regulation 2017/745/EU for a surface medical device that has limited (≤ 24 hours) contact with skin, and can be considered safe for use as indicated.

13. References

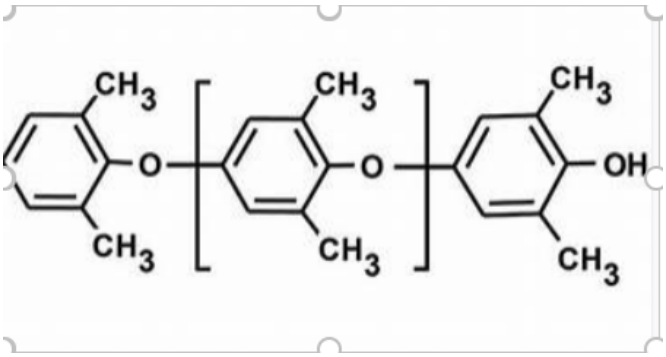
1.1 Report No. 15T 48244 03
1.2 Report No. 09T 31764 01
1.3 Report No. 09T 31764 02
1.4 Report No. 09T 32454 01
1.5 Report No. 09T 32454 02
1.6 Council Directive 93/42/EEC of 14 June 1993 concerning medical devices OJ L 169 of 12 July 1993
1.7 REGULATION (EU) 2017/745 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 5 April 2017
1.8 FDA Guidance for Industry and Food and Drug Administration Staff, June 16, 2016; Use of International Standard ISO 10993-1 “Biological evaluation of medical devices Part 1: Evaluation and testing within a risk management process”
1.9 Guidance for Industry and Food and Drug Administration Staff, September 4, 2020; Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"
1.10 ISO 10993-1 2009, Biological Evaluation of Medical Devices
1.11 ISO 10993-1 2018, Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process
1.12 ISO 10993-5:2009, Biological evaluation of medical devices Part 5: Tests for in vitro cytotoxicity
1.13 ISO 10993-10:2010, Biological Evaluation of Medical devices – Part 10: Tests for irritation and skin sensitization
1.14 ISO 10993-12:2012, Biological Evaluation of Medical devices – Part 12: Sample preparation and reference materials
1.15 ISO 14971:2012; Medical devices – Application of risk management to medical devices
1.16 ISO 14971:2019; Medical devices – Application of risk management to medical devices

Appendix 1 – Risk Analysis of Device Material

1. Polyphenylene Oxide

Polyphenylene oxide (PPO), also known as polyphenylene ether (PPE), is a thermoplastic, linear, noncrystalline polyether that is one of the most important engineering plastics due to its high strength, high heat distortion temperature, and high chemical resistance. Due to its heat and chemical resistant properties, this material is a stable material in use for medical device and is biologically stable and safe with negligible risk of degradation and leaching.

Its chemical structure is below:



2. Loctite 380 - Henkel

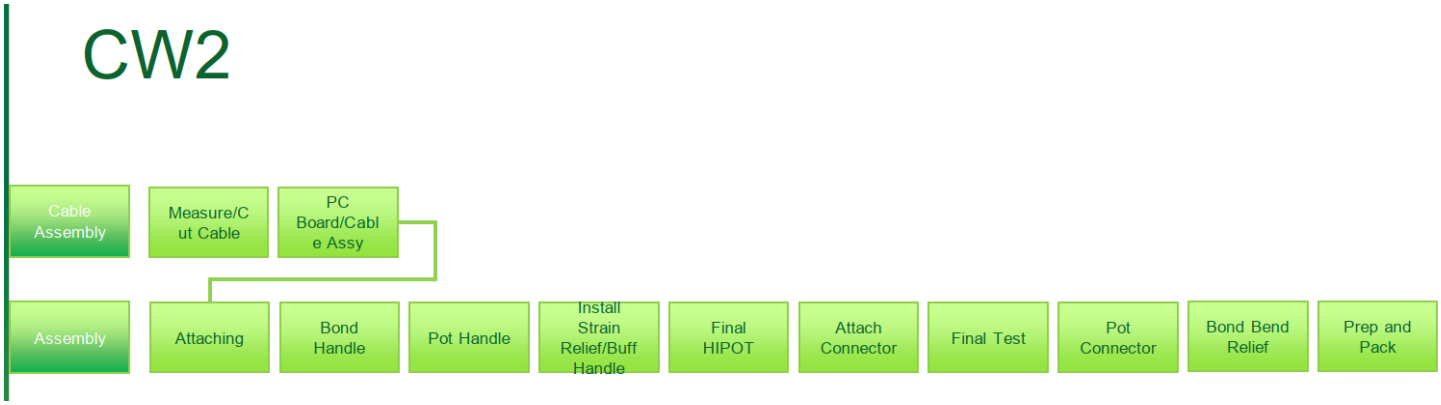
2.1 Cyanoacrylate Adhesive-CAS Number 7085-85-0

Cyanoacrylate adhesive has an established history of use in medical devices since 1970s with its use from tissue adhesives to scaffolds to implants to dental material and adhesives. Cyanoacrylate polymerize solely with moisture (presence of humidity) and its ability to self-cure at low temperature reduces the risk of exposing patients to volatile uncured compounds.

2.2 Carbon Black – CAS Number 1333-86-4

Carbon black is resent in Loctite 380 between 1-5%, Loctite 380 is also a very small percentage of the CW2 transducer. Loctite 380 is also a very small percentage of the CW transducer and at a low amount carbon black is considered by the FDA as an inert material per 40.CFR.180.930. Detail information is confidential but can be confirmed as proprietary by the supplier.

Appendix 2 – All Manufacturing Processes



Appendix 3 – Certificates of Analysis and Material Data Sheets

Please refer to the data sheets below.

Appendix 4 –Biocompatibility Testing Conducted

Use of biocompatible materials is the cornerstone to the fabrication of a biocompatible device. The processing of such materials into the device should not increase the risk of adverse biological effects. Biocompatibility testing is one approach that is recommended to evaluate the required biological safety endpoints.

The test samples used for all biocompatibility testing were comprised of materials used in the CW2 transducer. Testing were repeated in at three different time phases, all with acceptable data.

The CW2 transducers are designated as surface medical devices that have limited (≤ 24 hours) contact with skin when used as intended. The degree of testing required was dictated by the type and duration of patient contact as determined according to ISO 10993-1:2018. A summary of the biocompatibility testing performed is presented below.

Table 10: Summary of Biocompatibility Testing Performed

Current ISO Standard	ISO Standard Used in Testing	Test	Results	Study #
10993-5:2009	10993-5:2009	Cytotoxicity Study, ISO Elution Method	Non-cytotoxic	15T 48244 03
10993-10:2010	10993-10:2002	Sensitization Test	Non-sensitizer	09T 31764 01 09T 31764 02
10993-10:2010	10993-10:2002	Intracutaneous Irritation Study in Rabbits	Non-irritant	09T 32454 01 09T 32454 02

- **Cytotoxicity- MEM Elution Method (NAmSA Report Numbers: 15T 48244 03)**

  The test article was evaluated for potential cytotoxic effects to mammalian cells. This study was conducted following the guidelines of ISO 10993-5, Biological evaluation of medical devices - Part 5: Tests for *in vitro* cytotoxicity. The test article was not subdivided. Only the external surfaces with patient contact were included in the extraction. A single preparation of the test article was extracted in single strength Minimum Essential Medium (1X MEM) at 37°C for 24 hours using a ratio of 4gm/20mL of extraction media. The positive control, test article and control extracts were added at the same time to the culture plate in triplicate wells. Those plates were then incubated at 37ºC for 48 hours with 5% CO_2. The cultures were evaluated for cytotoxic effects by microscopic examination at 24 and 48 hours of incubation. The test article extract showed no evidence of causing cell lysis or toxicity.

- **Sensitization- Guinea Pig Maximization Method (NAmSA Report Number: 09T 31764 01 and 09T 31764 02)**

  The test article was evaluated for its allergenic potential or sensitizing capacity. This study was conducted based on the requirements of ISO 10993-10, Biological evaluation of medical devices - Part 10: Tests for irritation and skin sensitization. The test article was extracted in Normal Saline (SC) and sesame oil, NF (SO) using a ratio of 4gm/20mL of extraction media at 70ºC for 24 hours. The test and control animals were injected with the appropriate extract or control blank. Following a recovery period, the animals were topically patched with the appropriate test extract or control blank for 48 hours. Following 3 weeks rest period the animals were topically patched with the appropriate test extract and corresponding control blank for 24 hours. The dermal patch sites were observed for erythema and edema at 24 hours and 48 hours following patch removal. The test article was not considered a sensitizer in the Guinea pig maximization test.

- **Irritation- Intracutaneous Reactivity Method (NAmSA Report Number 09T 32454 01 and 09T 32454 02)**

The test article was evaluated for the potential to cause dermal irritation in rabbits. This study was conducted based on ISO 10993-10, Biological evaluation of medical devices - Part 10: Tests for irritation and skin sensitization. The test article was extracted in SC and SO using a ratio of 4g/20mL of extraction media at 37ºC for 24 hours or 70ºC for 24 hours. A 0.2 mL dose of the appropriate test article extract or vehicle control was intracutaneously injected into five separate sites along the right side of the dorsal mid-line, with the test article extract on one side and the vehicle control on the other. The injection sites were observed immediately after injection. Observations for erythema and edema were conducted at 24, 48, and 72 hours after injection. The test article met the requirements of the test since the difference between each test article extract overall mean score and corresponding control extract overall mean score was less than 1 for both the SC and SO test article extracts.

Appendix 5 - Systematic approach for biological evaluation of the medical device

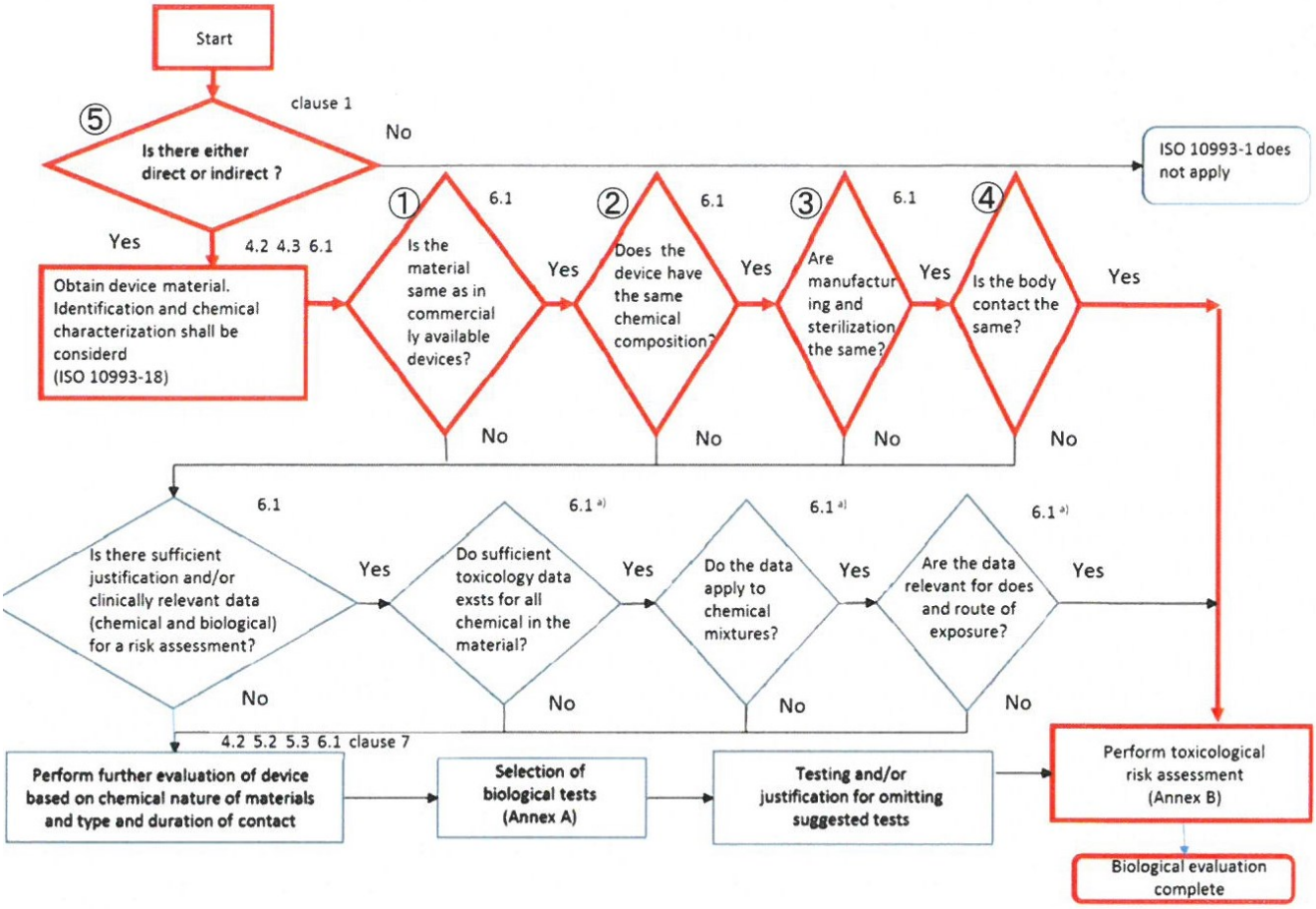


Figure 1 - Summary of the systematic approach to a biological evaluation of medical devices as part of a risk management process

- ① Is there either direct or indirect ? → Yes
- ② I Is the material same as in commercially available devices? → Yes
- ③ Does the device have the same chemical composition? → Yes
- ④ Are manufacturing and sterilization the same? → Yes
- ⑤ Is the body contact the same? → Yes

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