DECLARATION OF COMPLIANCE

WITH EN ISO 10993-1

Biocompatibility of the Test Material

MED610

Biocompatible Clear Material

Manufacturer:

Stratasys GmbH.
Airport Boulevard B 120,
77836 Rheinmünster

Germany

Scientific Background and Normative Requirements

The material MED610 is a UV-curable material to be used in a rapid prototyping (3-D printing) process using 3-D printing devices of Stratasys Ltd. Final devices are then intended to be used for various medical purposes including permanent skin contact (more than 30 days) and short term mucosal-membrane contact (up to 24 hours).

As notified by the manufacturer, two categories of 3-D printers may be used for printing and UV-curing of the investigational MED610 material [9]:

1. DESKTOP printers in HS, HQ and Draft modes equipped with 1 UV lamp and 2 printing heads (one for the MED610 model and one for the SUP 705 support). Final cleaning with IPA or 50:50 acetone:H_2O:

Material	Printer	Mode	Cleaning
MED610 printed with SUP 705	Alaris/Desktop Objet30 OrthoDesk Objet30 Dental Prime Objet30 Pro Objet30 Prime	HS & HQ	Cleaning with IPA or 50/50 acetone/ H_2O
		Draft	Cleaning with IPA

2. EDEN/CONNEX printers in HS, HQ and DM modes equipped with 2 UV lamps and 4 printing heads (8 channels). Final Cleaning with IPA:

Material	Printer	Mode	Cleaning
MED610 printed with SUP705	Objet260 Connex1/2/3 Objet260 Dental Selection Objet350 Connex1/2/3 Objet500 Connex1/2/3 Objet500 Dental Selection Connex260/350/500 Objet260 Connex Eden250/260V/260VS/ 260VS DA/350/350V/500V	HQ and HS DM (when available in printer)	Cleaning with IPA

As notified by the manufacturer Stratasys GmbH, MED610 can be manufactured from raw materials which are supplied by two different raw material manufacturers. Therefore, this Declaration of Compliance is intended to also evaluate a second source supplier and to assess whether final devices manufactured from both raw material suppliers will produce chemically and biologically identical 3D-printed products.

Furthermore, MED610 can be sterilized using both steam (132 °C for 4 minutes) and gamma irradiation (25 – 50 kGy). Therefore, additional testing was performed in order to cover these sterilization methods appropriately.

Medical devices intended for skin and mucosal membrane contact, including the MED610 rapid manufacturing medical devices are typically classified as a Class I, IIa or IIb medical devices under the Directive 93/42/EEC including Change Directive 2007/47/EC (Annex IX).

Based upon this intended use, and considering the related rapid prototyping processes the manufacturer Stratasys GmbH initiated a formal risk management process pursuant to EN ISO 14971:2009, in order to systematically evaluate, among others, any relevant biological risks.

For the risk assessment of biological risks, the procedures and provisions of prEN ISO 10993-1:2017 “Biological Evaluation of Medical Devices - Part 1: Evaluation and Testing within a Risk Management Process”, as well as FDA Guidance “Biological Evaluation of Medical Devices Part 1: Evaluation and Testing within a Risk Management Process", dated 16. June 2016, were applied. Based upon the criteria set out in this standard, the final products will typically be biologically classifiable as “surface devices” with “limited” (≤ 24 h), “prolonged” (24 hours – 30 days) or “permanent” (> 30 days) contact to “skin”. For body contacts to “mucosal membranes” or “breached or compromised surfaces”, a “limited” (≤ 24 h) or “prolonged” (24 hours – 30 days) contact to the human body would also be acceptable.

Therefore, in accordance with the aforementioned standard the following biological risks were particularly evaluated:

- Cytotoxicity	EN ISO 10993-5:2009
- Irritation	EN ISO 10993-10:2013
- Delayed type hypersensitivity	EN ISO 10993-10:2013
- Genotoxicity	EN ISO 10993-3:2014
- Chemical characterization	EN ISO 10993-18:2009
- USP Plastic Class VI	USP 34 <88>

For sample preparation and dosing EN ISO 10993-12:2012, respectively USP 34 <88> is applicable.

All other risks mentioned in EN ISO 10993-1, including serious risks like systemic toxicity (acute, subchronic, chronic), genotoxicity, carcinogenicity, reproductive and developmental toxicity, biodegradation, toxicokinetics and immunotoxicity are deemed not relevant, respectively not applicable. This assessment is based upon a risk assessment performed by Stratasys GmbH in terms of EN ISO 14971 and considers the chemical nature of the device and potentially leachable substances that may be released from the device during its intended use (type and duration of body contact). Therefore, and following the principles and procedures set out in EN ISO 10993-1, no scientific or experimental data regarding these additional biological risks are provided for the medical devices manufactured through the aforementioned rapid prototyping process.

This biological evaluation was prepared in view of the fact that Stratasys GmbH uses several raw materials suppliers. Furthermore, polymerized MED610 devices may be sterilized using steam (132 °C for 4 minutes) or gamma irradiation (25 – 50 kGy). Therefore, appropriate testing was performed in order to cover these modifying product variants appropriately.

The assessment of the aforementioned biological risks for the polymerized MED610 variants under investigation showed the following results:

Document History

Version 1: Basic Declaration of Conformity dated 19 July 2011

Version 2: Amended Declaration of Conformity dated 12 August 2011 after AMES test results become available

Version 3: Amended Declaration of Conformity dated 18 August 2012 including the new desk-top printers high speed mode and related test results

Version 4: Due to the merger of Stratasys Ltd. and Objet Ltd. the company name in the Declaration of Conformity dated 10 April 2013 were changed into Stratasys Ltd..

Version 5: Change of manufacturer address from Stratasys Ltd, Israel to Stratasys GmbH, Germany and correcting of type and duration of body contact dated 26 June 2013

Version 6: Justification of second source raw materials and modified manufacturing method using the support substance SUP 705 for printing with DESKTOP, respectively, EDEN/CONNEX printers. Document date 11 November 2015

Version 7: Amended Declaration of Compliance dated 24 February 2017 with reference to further non-clinical investigations for additional printer mode combinations performed by the manufacturer Stratasys Ltd.

Version 8: Amended Declaration of Compliance dated 23 January 2018 with reference to further non-clinical investigations for additional sterilization methods (steam and gamma) and justification of second source raw materials as applied by the manufacturer Stratasys Ltd.

Quality Assurance

The undersigned declares that he is suitably qualified for the preparation of this Biocompatibility Assessment and able to show objectivity as an independent expert for the medical device industry (see attached CV). The undersigned declares that he was unbiased when writing this Declaration of Compliance and that he was not influenced by the manufacturer or anybody else in his conclusions.

Furthermore, the authors declare that this Biocompatibility Assessment was performed in compliance with the quality management system according to EN ISO 13485, as established by the contractor md registration support Ltd., Grenzenstrasse 13, 88416 Ochsenhausen, Germany (see attached certificates). There were no circumstances that may have affected the quality or integrity of this Biocompatibility Assessment.

2018-01-30

Dr. Dieter R. Dannhorn, 2018-01-30
Scientific Director

Biocompatibility Assessment

Cytotoxicity

In a first series of tests, the potential of cytotoxicity of the of polymerized MED610 was investigated in compliance with a quality management system according to EN ISO/IEC 17025, using the biological in vitro cytotoxicity test with L929 mouse fibroblasts in accordance with EN ISO 10993-5 (mdt reports 10z125 [1]; 11z095 [8]; 14z207 [10] for second source raw materials; UL MDT report 11406569 1.1 [16] further printing mode variants). For sample preparation, the provisions of EN ISO 10993-12 were fulfilled. The materials were extracted for 24 hours at 37 °C with sterile culture medium containing 10 % fetal calf serum at a ratio of 1.25 cm^2.

In summary, the tested material MED610 showed no cytotoxic effects after dynamic extraction in culture medium. Under the conditions of the test, the undiluted extracts of the MED610 (100% value) caused growth inhibition values of 14 -33 %, respectively 16% (second source raw materials). These growth inhibition values correspond to a biological reactivity score value of “0” - “1” according to USP 40 <87>.

In the course of a modification of the manufacturing process, the support substance SUP705 was introduced. Therefore, cytotoxicity testing was repeated with MED610 and SUP705 using the DESKTOP Prime printer in HQ Mode (UL MDT report 10889736 1.1, [11]) and CONNNEX 3 in Digital Material Mode (UL MDT report 10799362 1.1, [12]). In summary, using identical cytotoxicity test conditions as compared to previous testing (see above), the tested MED610 and SUP705 materials caused growth inhibition values of 16% (DESKTOP printer HQ mode) and 20 % (DESKTOP printer HS mode), respectively 30% (CONNEX printer digital material mode).

In a recently performed test series, polymerized MED610 with SUP705 was investigated after steam sterilization (132 °C for 4 minutes; UL MDT report 11885997 1.1 [18]) and after gamma sterilization (25 – 50 kGy; UL MDT report 11885997 2.1 [19]). Furthermore, another second source was evaluated in comparison to the primary source (UL MDT report 11885997 3.1 [20]). In summary, using identical cytotoxicity test conditions as compared to previous testing (see above), the tested MED610 and SUP705 materials caused growth inhibition values of 18% (steam sterilization), 14 % (gamma sterilization) and 11 % (primary source materials) / 8 % (second source raw materials).

According to EN ISO 10993-5, growth inhibition values of less than 30 % are considered to be clinically irrelevant. According to USP 40 <87>, reactivity values of 0 - 2 are considered acceptable for medical devices.

Based upon the observed results and under the test-conditions chosen, all investigated MED610 materials with and without SUP705 and considering various sterilization methods (no sterilization, steam and gamma sterilization), are evaluated to cause no clinically relevant growth inhibition, as requested by EN ISO 10993-5, if manufactured appropriately and in compliance with the manufacturer’s instructions.

Irritation

For polymerised MED610 no animal experimental irritation study was conducted, because the available cytotoxicity test (see above), USP Plastic Class VI testing (see below) and chemical fingerprint investigations (see below) indicate that no irritation potential is to be expected. Therefore, and considering the animal protection regulations according to EN ISO 10993-2, an animal experimental irritation study as requested by EN ISO 10993-10 was not justifiable.

Based upon the aforementioned study results and scientific arguments it is concluded that polymerised MED610 has no irritant potential in terms of EN ISO 10993-10.

Delayed Type Hypersensitivity

The sensitising potential of polymerised MED610 was investigated in compliance with a quality management system according to EN ISO/IEC 17025, using the Guinea pig maximization test for delayed-type hypersensitivity according to Magnusson and Kligman in accordance with EN ISO 10993-10. Pursuant to the requirements of EN ISO 10993-12, both polar (mdt report 10b097A, [2]) and non-polar extracts (mdt report 10b097B, [3]) were investigated. For sample preparation, the provisions of EN ISO 10993-12 were fulfilled. The materials were extracted under agitation with 0.9 % saline solution respectively cottonseed oil at a ratio of 3 cm^2 per ml. In this test, polymerised MED610 derived from raw material provided by the previous supplier was used.

In summary, none of the tested polar and non-polar extracts of the investigated test materials caused any reactions identified as sensitization. The sensitization rate after application of the respective extracts was 0%.

Alternative final products manufactured with SUP705, from “second source”, and test samples subjected to steam sterilization or gamma sterilization, were not individually tested for their sensitization potential, based upon the material characterization data obtained from polymerized “primary source”, “second source MED610 raw materials and polymerized components subjected to steam sterilization and gamma irradiation. This is justified by the fact that these various test samples were found to release comparable profiles of leaching substances to the respective extraction vehicles. Therefore, animal experimental testing of these variants of polymerized MED610 materials was not justifiable, considering the provisions of EN ISO 10993-2.

Therefore, it is concluded that medical devices manufactured from MED610 raw materials with or without SUP705, obtained from “primary” and “second source” suppliers, as well as subjected to various sterilization conditions (no sterilization, steam sterilization, gamma sterilization), do not have any sensitizing potential pursuant to the requirements of EN ISO 10993-10.

USP Plastic Class VI Testing

The biological reactivity of polymerized MED610 was investigated in compliance with a quality management system according to EN ISO/IEC 17025, using the USP Plastic Class VI test regimen pursuant to USP 34 <88> (mdt report 10b096, [4]). For sample preparation and control materials, the provisions of the aforementioned USP regulation were fulfilled. Four extracts of the test material were prepared and applied: Isotonic saline solution, 5% ethanol in saline solution, polyethylene glycol 400 and cotton-

seed oil. Appropriate extracts were used for systemic injection (intraperitoneal and intraveneous administration) and for intracutaneous testing. Sterile test items were used directly for implantation testing. In this test, polymerised MED610 derived from material provided by the previous supplier was used. In summary,

- In the Systemic Injection Tests no significant clinical signs were observed in the test animals;
- In the Intracutaneous Test, the test animals showed no irritant effects;
- In the Implantation Test no compound-related tissue reactions were found in the test animals.

Based upon the results obtained in these studies, it is indicated that the tested polymerized MED610 material meets the requirements of USP Plastic Class VI.

Alternative final products manufactured with SUP705, from “second source”, and test samples subjected to steam sterilization or gamma sterilization, were not individually tested for compliance with the USP Plastic Class VI requirements, based upon the material characterization data obtained from these particular product variants. This is justified by the fact that these test samples were found to release comparable profiles of leaching substances to the respective extraction vehicles. Therefore, animal experimental testing of these variants of polymerized MED610 materials was not justifiable, considering the provisions of EN ISO 10993-2.

Genotoxicity

The potential of genotoxicity of the test material (old and new formulation) has been investigated in compliance with a quality management system according to EN ISO/IEC 17025, using the Salmonella typhimurium reverse mutation assay test procedure in accordance with EN ISO 10993-3 (mdt project 11b049-A [6] and 11b049-B [7]). For sample preparation, the provisions of EN ISO 10993-12 were fulfilled. The materials were extracted with 0.9 % saline solution respectively DMSO for 72 h at 37 °C and at a ratio of 3 cm^2.

In summary, under the conditions of this test, the investigated material extracts (old and new) did not cause any pair changes or frameshifts in the genome of the used Salmonella typhimurium tester strains.

Based upon these results and considering the favourable results of the aforementioned biological tests as well as physico-chemical material characterization data provided in the Chapter “Gaschromatographic Fingerprint Investigations” (see below), no other tests for genotoxicity, as requested by EN ISO 10993-3, were deemed necessary in order to finally judge on the genotoxicity potential of the MED610 (primary and second source raw material suppliers) with and without SUP705 and subjected to different sterilization conditions.

Therefore, the investigational polymerised MED610 printed with SUP705 is considered to have no genotoxic properties pursuant to the requirements of EN ISO 10993-3.

Gaschromatographic Fingerprint Investigations

In order to investigate potential organic leachable substances which may be released from the polymerised MED610, a first series of 3D-printed materials was subjected to an aqueous and organic extraction followed by GC/MS analyses of the respective extracts (mdt reports 11y181 [5], 14y311 for second source raw materials [13]).

More recently, the manufacturer introduced an additional support substance, SUP705, which was similarly investigated with regard to its impact on leachable substances as compared to MED610 without SUP705 (UL MDT reports 10799362 2.1 [14]; 10889736 2.1 [15]; UL MDT report 11406569 2.1 [17] for further printing mode variants).

In a final series of tests, polymerized MED610 with SUP705 was investigated after steam sterilization (132 °C for 4 minutes; UL MDT report 11885997 5.1 [21]) and after gamma sterilization (25 – 50 kGy; UL MDT report 11885997 6.1 [22]). Furthermore, another second source was evaluated in comparison to the primary source (UL MDT report 11885997 7.1 [23]).

The studies were performed in compliance a quality management system according to EN ISO/IEC 17025, respectively, in compliance with international GLP regulations, and served the scope of a material characterization as requested by ISO 10993-18.

For sample preparation, the provisions of EN ISO 10993-12 were fulfilled. The dynamic extraction was performed for 72 h at 37°C and at a ratio of 3 cm^2 per ml using the following extraction media: water, isopropyl alcohol, and n-hexane. After the extraction of the test material, aliquots of the extraction media were analyzed by means of GC/MS. In case of peaks recorded in the chromatograms, the mass spectra of the peaks were checked for analogies in a MS library in order to chemically identify the substances, preferably by CAS numbers.

In summary, the GC/MS fingerprint investigation of the various test materials and manufacturing variants resulted in similar patterns for leaching substances:

- No semi-volatile organic compounds were detected in the GC/MS fingerprint chromatograms of the water extracts of all investigated test materials (MED610 primary and secondary suppliers, MED610 printed with or without SUP705, manufactured from various printers and subjected to various sterilization conditions).
- In the GC/MS fingerprint chromatograms of the n-hexane extracts of the investigated test materials similar amounts of leaching Isobornyl acrylate (CAS 5888-33-5) and 1-Benzoylcyclohexanol (CAS 947-19-3) were detected.
- Numerous product-related organic substances, representing similar peak patterns, were detected in the GC/MS fingerprint chromatograms of the isopropyl alcohol extracts of the investigated test materials. These substances were, however, not further evaluated as isopropyl alcohol does not represent physiological extraction conditions.

The aforementioned results allow the following conclusions:

1) Medical devices manufactured from MED610 raw materials using appropriate 3-D printers with and without SUP705 are intended for long term skin contact (more than 30 days) and limited mucosal-membrane contact (up to 24 hours). Therefore, the results obtained after extraction with water (representing polar body environments) and with n-hexane extracts (representing non-polar body environments) are of particular importance. The results obtained from undiluted isopropyl alcohol extracts do not reflect the intended physico-chemical properties of the human body. Therefore, these results are less relevant for the assessment of biological properties of the extracted test samples.
2) All investigated test materials and manufacturing variants presented with identical results in the analysed water extracts. No organic leachable substances were detected under the conditions of the test.
3) The investigated test materials and manufacturing variants presented with well comparable results in the analysed n-hexane extracts. The investigated extracts presented with comparable amounts of isobornyl acrylate (CAS 5888-33-5) and Irgacure 184 (CAS 947-19-3), or in some variants, no leachable substances were identified (see UL MDT report 11406569 2.1 [17]).
4) The investigated isopropyl alcohol extracts also presented with similar, however not identical, chromatographic results, showing similar profiles of organic leachable substances.

Based upon these study results, all investigated MED610 UV cured materials (primary and secondary suppliers) and investigated 3-D printers and printing modes, with and without SUP705 and subjected to various sterilization conditions (no sterilization, steam sterilization and gamma sterilization) can be evaluated to deliver substantially equivalent final medical devices. Therefore, further animal experimental testing with alternative variants of polymerized MED610 products, could not be justified, considering the animal protection regulations as of EN ISO 10993-2.

Conclusion

Based upon the aforementioned study results and evaluation arguments and considering the provisions of the current version of prEN ISO 10993-1:2017, as well as FDA Guidance "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing within a Risk Management Process", dated 16. June 2016, it is concluded that UV cured MED610 materials, manufactured from primary and second source raw material suppliers, printed with or without SUP705, manufactured on appropriate DESKTOP and EDEN/CONNEX 3D-printers and subjected to various sterilization conditions (no sterilization; steam sterilization with 132 °C for 4 minutes; gamma sterilization with 25 – 50 kGy), can be evaluated biocompatible if manufactured appropriately and applied in compliance with their intended purpose as outlined in the manufacturer's Instructions for Use.

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2018-01-30

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Attachment (page 14 of this document)

Certificate

mdc medical device certification GmbH
certifies that

md registration support Ltd.
Grenzenstraße 13
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Germany

for the scope

regulatory advisory services for medical devices

has introduced and applies a

Quality Management System

The mdc audit has proven that this quality management system
meets all requirements of the following standard

EN ISO 13485

Medical devices – Quality management systems –
Requirements for regulatory purposes

EN ISO 13485:2012 + AC:2012 - ISO 13485:2003 + Cor. 1:2009

Valid from	2013-06-28
Valid until	2018-06-28
Registration no.	2190.58.01/0
Report no.	E 2190.58 / 2013-06-28
Stuttgart	2013-06-28

Head of Certification Body

Akkreditiert durch
Zentralstelle der Länder für Gesundheitsschutz bei Arzneimitteln und Medizinprodukten
ZLG-ZQ-976.00.03-46

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- 1979-89: University studies of biology and English language, PhD in Biology
- 1991-94: Clinical Project Management for Hoechst AG / Cassella AG in Frankfurt/M. Responsible for clinical development of a novel antifungal drug (vaginal, oral and dermal application)
- 1994-96: Manager Development Germany for Alcon Pharma GmbH in Freiburg / Alcon Laboratories (Fort Worth, Texas); responsible for the all development activities (testing and preparation of submission files), of ophthalmic pharmaceuticals and medical devices
- 1996-97: Scientific Director for the Dr. Müller-Lierheim GmbH with particular responsibility for the testing activities
- 01/1997-04/2013: General Manager of mdt medical device testing GmbH in Ochsenhausen. The company has been accredited from the German Zentralstelle der Länder für Gesundheitsschutz (ZLG) for clinical and non-clinical testing of medical devices. The company's main focus is on physical – chemical testing, biological and microbiological testing and clinical investigations of medical devices
- 01/2000: Management buyout and purchase of 100 % of the shares of mdt medical device testing GmbH.
- 03/2005: Foundation of md registration support Limited. Owner of 100% of the shares. The company provides registration support to medical device manufacturers, consultation, training and expert opinions
- 08/2011: Transfer of all mdrs shares to UL International (Netherlands) B.V.
  Dr. Dannhorn remained General Manager of the company until 03/2013
- 08/2011: Transfer of all mdt shares to UL International Germany GmbH
  Dr. Dannhorn remained General Manager of the company until 04/2013
- Until 07/2013: Member of the
  - German Association for pharmaceutical Medicine e.V. (DGPharMed)
  - Regulatory Affairs Professionals Society (RAPS)
  - Bundesverband medizinischer Auftragsinstitute (BVMA) e.V.
- Service in various medical device standards committees respectively national working groups:
  - CEN/TC 170 - ISO/TC 172: 'Ophthalmic Optics and Instruments' (contact lenses, intraocular lenses) (1997 – 2004)
  - CEN/TC 285 - ISO/TC 194: 'Biological Evaluation of Medical Devices' (focusing on EN ISO 10993 series of standards) (1997 – 2003)
  - CEN/TC 285 - ISO/TC 194 WG 4: Revision of ISO 14155 for clinical investigations of medical devices (1999 – 2010).
- Since 1996 continuously working in the medical device area (industry, test laboratory, standardization) with focus on performance and safety of medical devices.
- Since 1998: Avocation as an independent expert for various German Notified Bodies: Preparation of evaluation reports regarding biological, microbiological and clinical performance and safety of medical devices
- Since 2009: Lectureship at the University Clinic Ulm in the curriculum “Advanced Materials”
- Since 08/2013: Freelance expert and management consultant for mdt medical device testing GmbH, md registration support Ltd. and more general for the medical device industry
- A list of publications, abstracts and seminars is available on request

Date (yyyy-mm-dd): 2018-01-30 Signature: