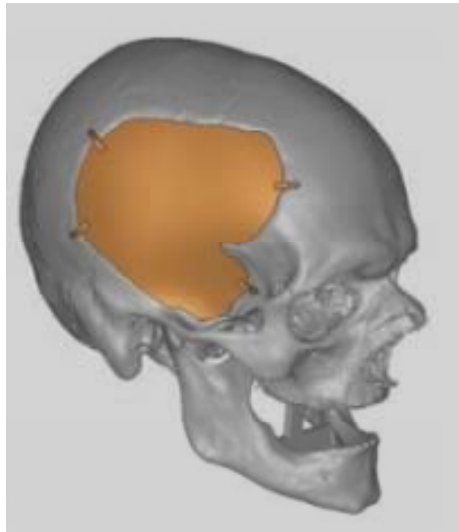


"Biomedical Polyurethane Developed Within the Custom-IMD Project"

Dr Steve Rowlands.

Smithers Rapra Technology.



CUSTOM-IMD



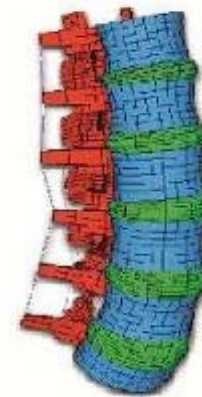
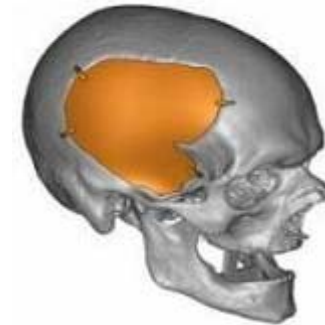
Contents



1. Introduction to the Custom IMD Project.
2. Polyurethane for a Spinal Nucleus Prosthesis.
3. Summary.

Introduction

- Custom-IMD is a 6th Framework programme funded in part by the EU.
- There are three main case studies within Custom-IMD.
 - 1. Cranio-facial bone plate prosthetic,
 - 2. Spinal lumbar nucleus prosthetic,
 - 3. Dental restoration.



Project Overview

Objective: development of the complete e-supply chain for the realization of custom implants and to demonstrate those through the 3 applications :

Areas of work include:

- Materials development
- "Rapid" Manufacturing
- Biocompatibility
- Data acquisition
- Implant design

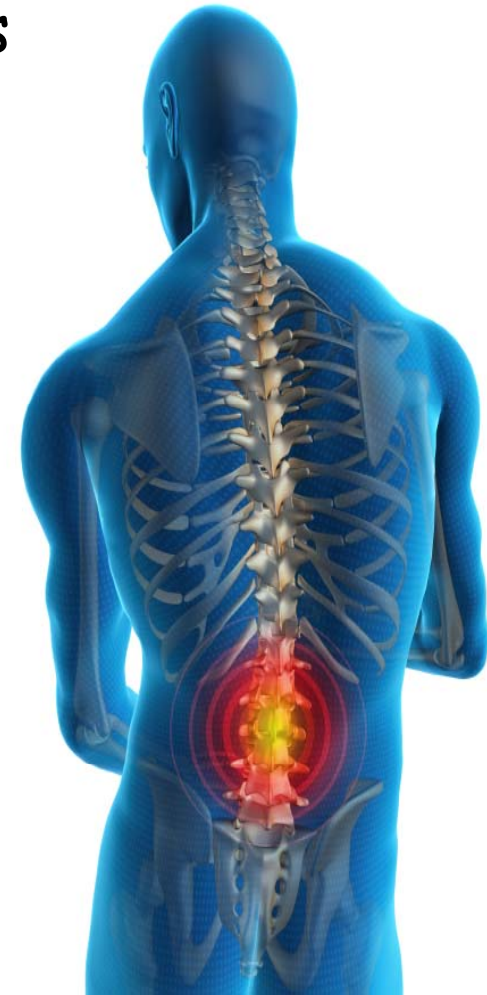
➤ e-Supply chain

Project Overview: *The Numbers*

- Budget: € 9,8M with € 5,4M of EU funding
- Duration: 48 months (from 01.02.07 to 31.01.11)
- Partners: 23
 - RTD: 4
 - SME: 16
 - University Hospital: 2
 - Centre of excellence: 1
- Countries: 7
 - Belgium
 - Germany -Switzerland
 - Netherlands -Spain
 - Poland -United Kingdom

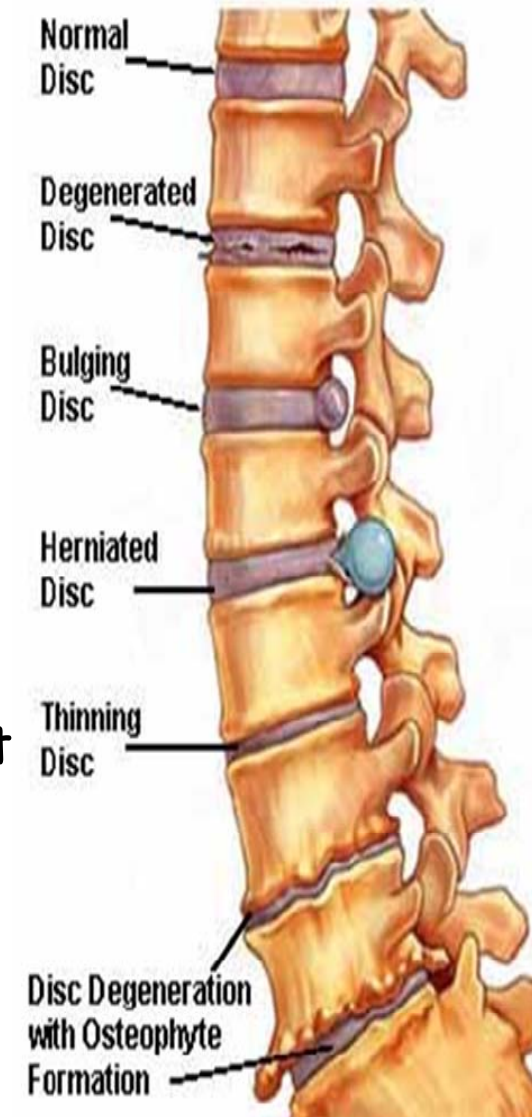
Polyurethanes for Spinal Disc Restoration

- The spinal implant investigation focuses on a **nucleus** implant for the **lumbar** region only.
- Polyurethane development and Optimisation studies have been targeted for the Spinal Nucleus Implant.
- Specific Mechanical, Chemical and Material properties were therefore required.

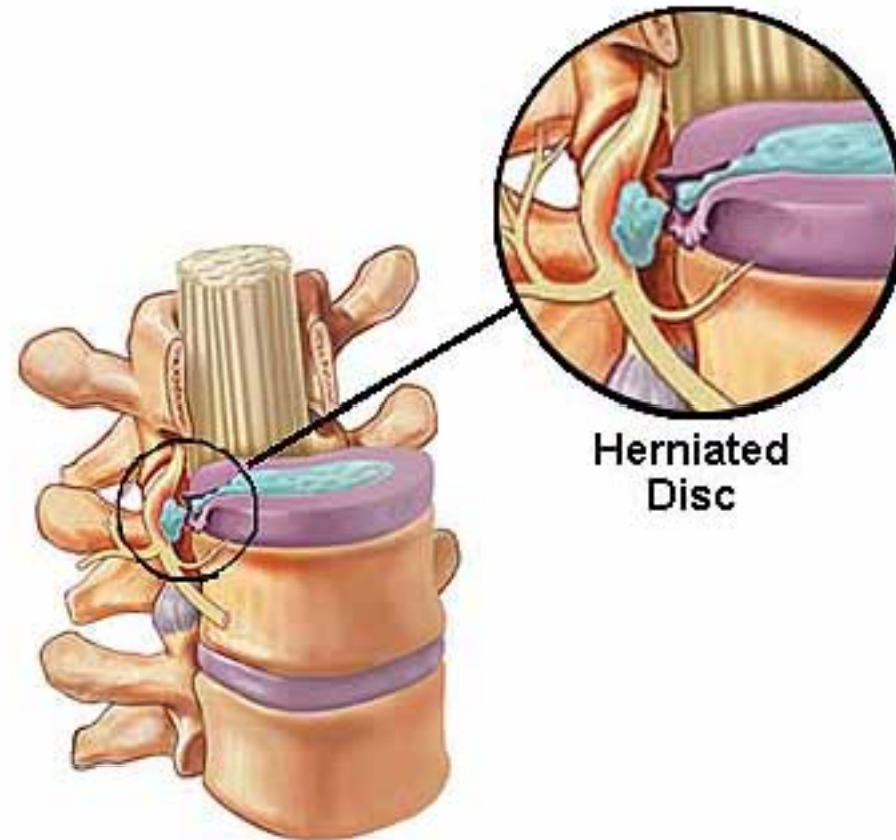
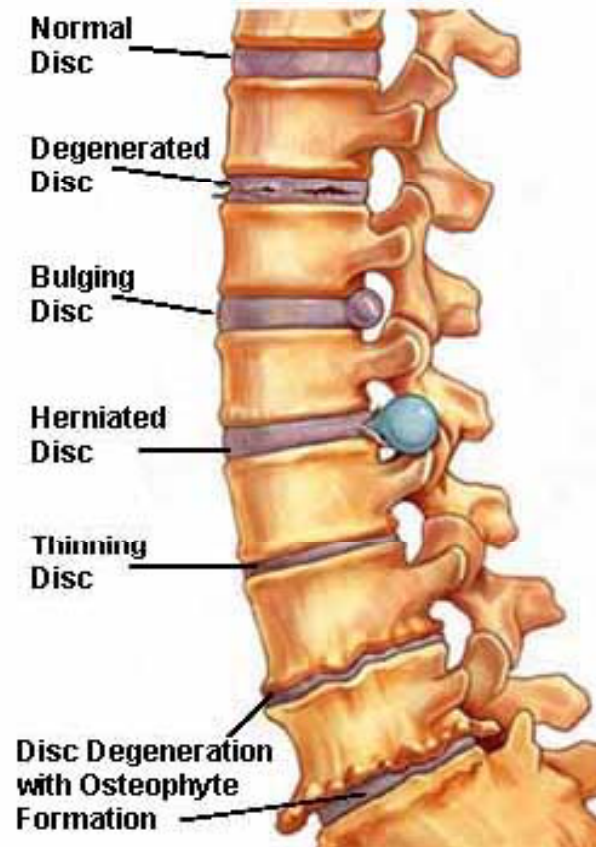


Why a Spinal Nucleus Implant?

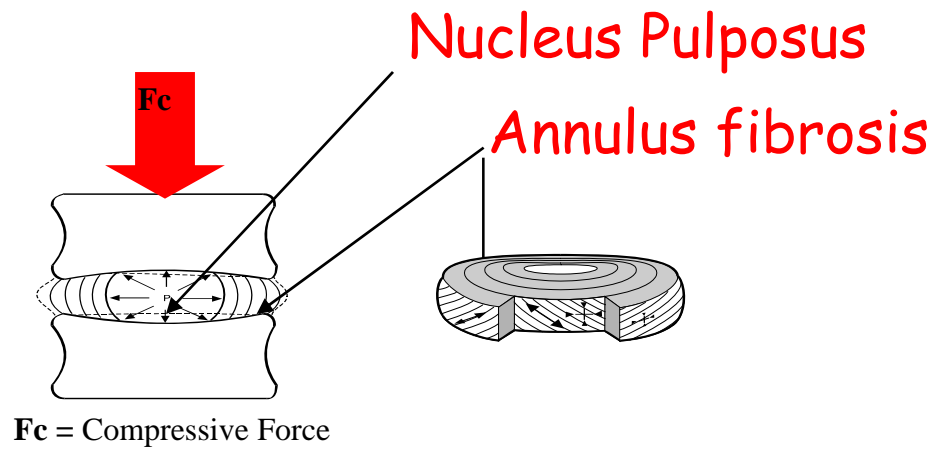
- **Degenerative disc disease** refers to a syndrome in which a compromised disc causes low back pain.
- The pain is also frequently caused by simple wear and tear on the spine.
- Degenerative disc disease is fairly common, and it is estimated that **at least 30% of people aged 30-50 years old** will have some degree of disc space degeneration.



Examples of Spinal Disc Problems



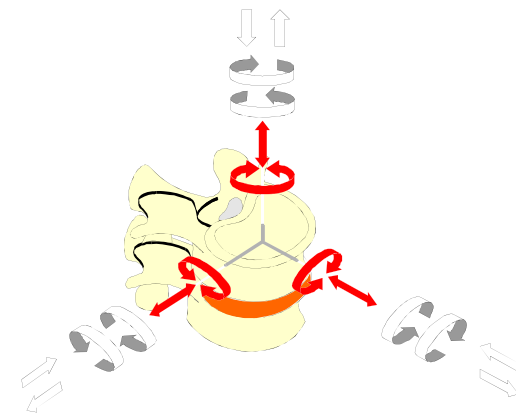
Polyurethane for a Spinal Nucleus Prosthetic



Kinematics of the Natural Disc

In order to reproduce physiological kinematic behaviour the following criteria must be observed:

- 6 degrees of freedom.
(3 translations and 3 rotations)
- Allow movement without exceeding the natural range of movement.
- Avoiding implant migration.
- Floating centre of rotation as in the natural spine.
- Maintain disc height during motion.



6 degrees of spinal motion

Dynamics and Endurance of the Natural Disc.

The maximum expected in vivo compression load in the lumbar discs during daily activities are:

- Normal Standing up: 700 - 1000 N
- Standing up with trunk flexed 30°: 2400 N
- Sitting: 1800 - 2700 N
- Bending forward and lifting a 20 kg load: 4000-4200 N

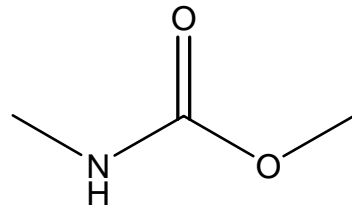
Intradiscal compressive stresses (typical adult) during daily activities are:

- Standing: 0.2 - 1.1 MPa
- Sitting: 0.4 - 1.5 MPa
- Dynamic and weight bearing motions: up to 2.5 MPa
- Estimated Young's Modulus (from FEM models) for a nucleus is: up to 4.2 MPa

Polyurethane Material Requirements

General PU Chemistry

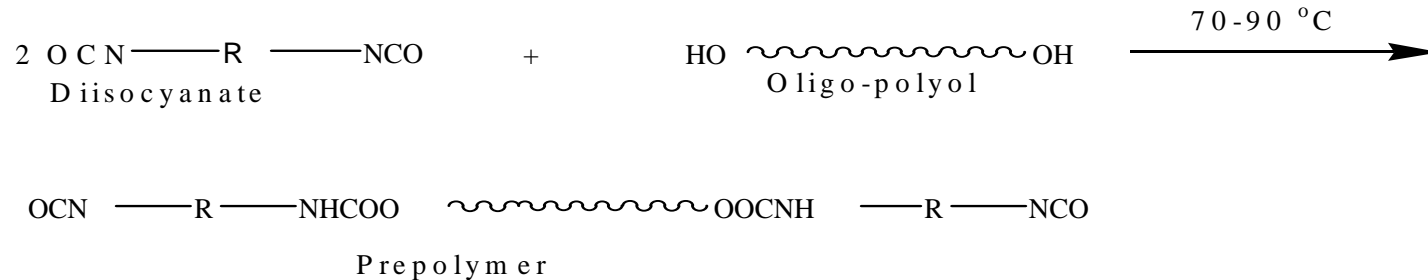
- Polyurethanes are a common commercial polymer and can possess diverse properties depending on how they are manufactured. They are characterized by containing the repeat unit:



- PU's generally have hard and soft segments. In one way, they can be considered both amides and esters of carbamic acid (carbamates). The repeat unit is usually synthesized by addition of an active hydrogen containing species across the carbon-nitrogen double bond of an isocyanate.

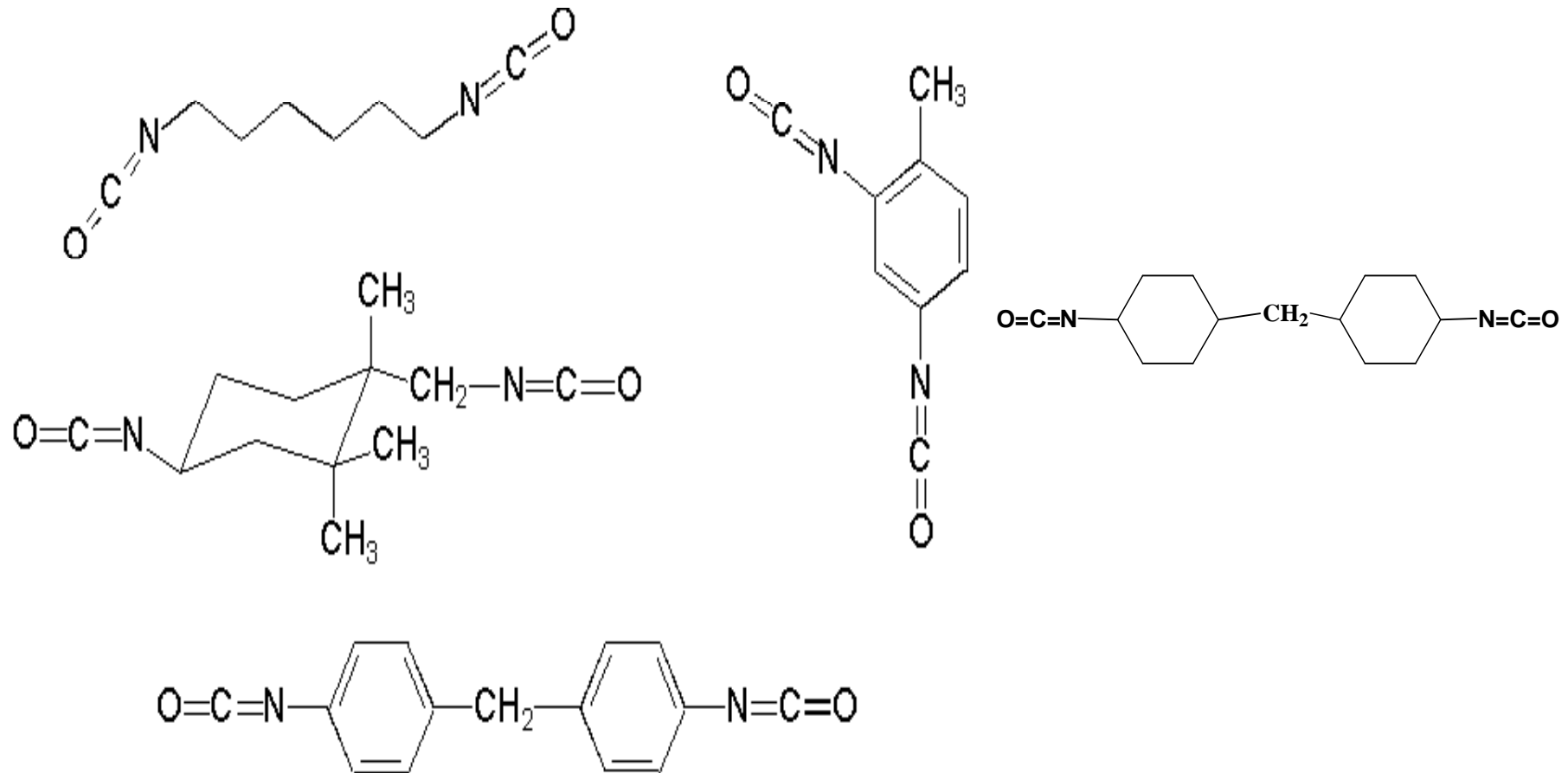
Isocyanate/Polyol Reaction Forming a Linear TPU

- A di functional isocyanate reacting with a diol will yield a linear and therefore thermoplastic polyurethane, (TPU).
- A medium Mw diol (~400-2500 Daltons) is reacted with the diisocyanate yielding a pre polymer as illustrated below.



- By the reaction of the pre polymer with a chain extender such as ethylene glycol, 1,4-Butane diol or a diamine, the high Mw polymer is formed.

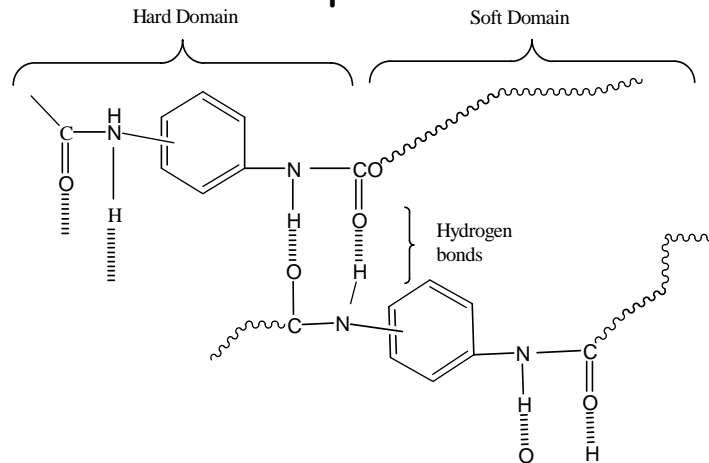
Typical Isocyanates for PU Manufacture



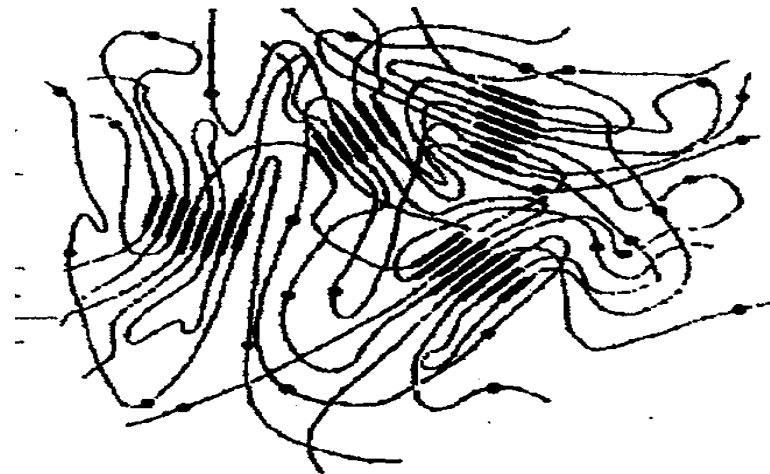
Top left-1,6, hexamethylene di-isocyanate (HDI): **middle-right**-2, 4-Toluene isocyanate (TDI):
middle-left; Isophorone diisocyanate: **bottom**-4,4' methylene bis(phenyl isocyanate), MDI, and **far
right**, Hydrogenated MDI, 4,4' methylene bis(cyclohexane diisocyanate).

Segmented PU

- The urethane and/or urea linkages with the extender species, because of the possibility of hydrogen bonding, generate the "hard" domain or "hard segment" of the PU elastomer as illustrated below.
- The high mobility of high Mw polyol chains represent the "soft segment" and ensure the high elasticity of the resulting PU elastomer. This structure is virtually cross linked by secondary (hydrogen) bonds. At higher temperatures the hydrogen bonds are destroyed and therefore at high temperatures it is possible to process the linear PU elastomers in the melt state, similar to all common thermoplastics.



The hard and soft domains of PU elastomers

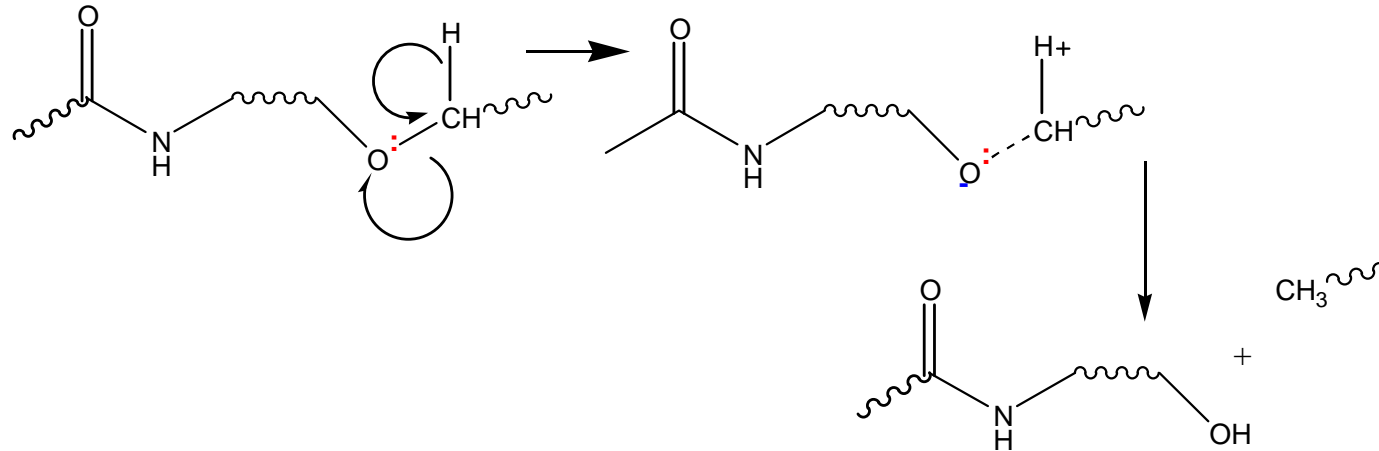


Soft Segment Structure

- Studies have shown that some PU elastomers (ester-based) were not suitable for long term implantation due to poor hydrolytic stability.^{[1] [2]}
- The problem was thought to be addressed to some degree by the use of polyether macro diols. Polyteramethylene oxide (PTMO) macro diols being a favourite choice, but these are susceptible to oxidative degradation^[3].
- The degradation appears as surface cracking, stiffening and erosion or deterioration of the mechanical properties such as flex fatigue resistance.
- Biodegradation may also lead to leachable toxic products.

Oxidative Degradation

- It is likely that the biological chemical agents derived from the host implant response are oxidative and that susceptible functionalities such as abstractable methylene hydrogen atoms adjacent to oxygen in the PTMO macrodiol are the points of attack [4].
- This theory is reinforced by the observation of enhance bio stability in the presence of antioxidants.



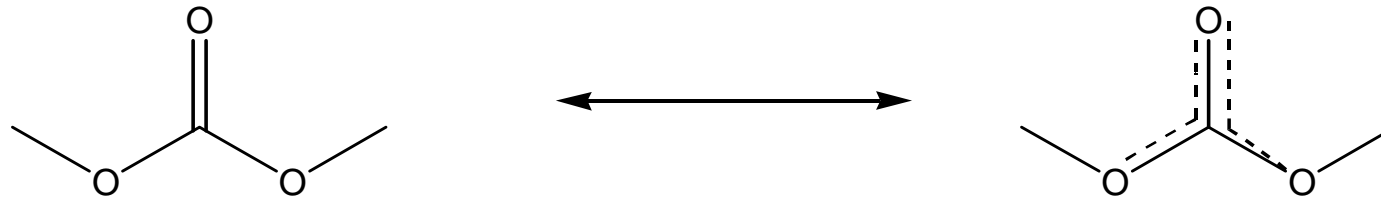
The scission products may cross link to adjacent chains, therefore the TPU becomes harder and brittle, with a change in Mw.

Polycarbonate Macro Diols

- Use Polycarbonate diol as the soft segment.
- Esterase Enzymic attack of the polycarbonate moiety has been reported.
- However polycarbonate soft segments are thought to be the most attractive avenue for chronic bio stable PU implants.
- The polycarbonate shows enhanced biostability over polyester urethanes for two main reasons.

Stability of Carbonate Group.

(i) The polycarbonate has a pseudo π -bonding system, thus stabilising the carbonate moiety against attack, as shown below.



The delocalised pi system for polycarbonate

(ii) Hydrolysis of the carbonyl moiety is acid catalysed.

Hydrolysis of an ester yields an alcohol and an acid, thus the reaction becomes self catalysed, whereas hydrolysis of the carbonate group yields CO_2 and an alcohol, leading to slower reaction kinetics.

Stability of Carbonate Group (Cont.)

- So why use PU if it's so difficult to achieve chronic (50 yrs +) biostability?
- PU is used for it's excellent mechanical versatility.
- The material's bulk properties determines the specific mechanical requirements.
- The surface chemistry governs the biostability.
- Therefore modify surface to protect the vulnerable soft segment.

Self Assembling Monolayer End-Groups (SAME)-(PTG).

- Generally, a material is designed for its bulk properties but its **surface chemistry is what determines the biocompatibility**. SAME technology offers a solution to this problem.
- SAMEs may be **engineered into medical polymers during synthesis** to provide a robust, built-in surface chemistry that self-assembles after device fabrication. More than one SAME may be used on a single polymer.
- Therefore the **bulk polymer may determine characteristics** such as mechanical integrity while **the SAME determines the surface biostability**.

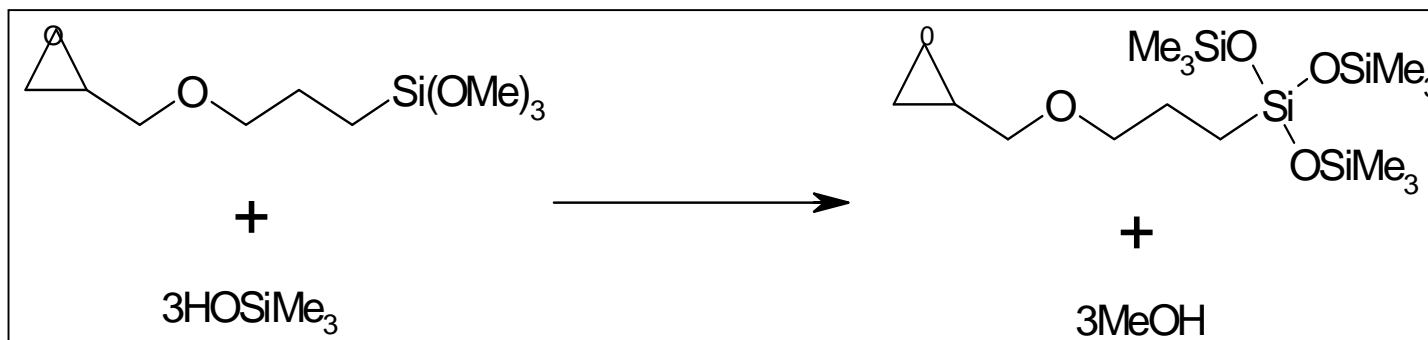
Self Assembling Monolayer End-Groups (SAME)-(PTG). (cont.)

- SAMEs have the advantage over self assembled monolayers (SAM) in that they are designed to covalently bond with the surface of the bulk polymer, thus **enabling in vivo environmental stability**. E.g. a SAME-modified polycarbonate urethane using an octadecane end group.
- This technology has been developed at the Polymer Technology Group (PTG) in Berkley, CA and may be one solution to long term biostability/biodurability.

Reactive Processing of PU

- Another way of functionalising PU in order to provide an **enhanced biostable and/or functionalised surface chemistry** is to react the PU in the melt with various reactive species.

Epoxide ring opening followed by a siloxane exchange reaction.



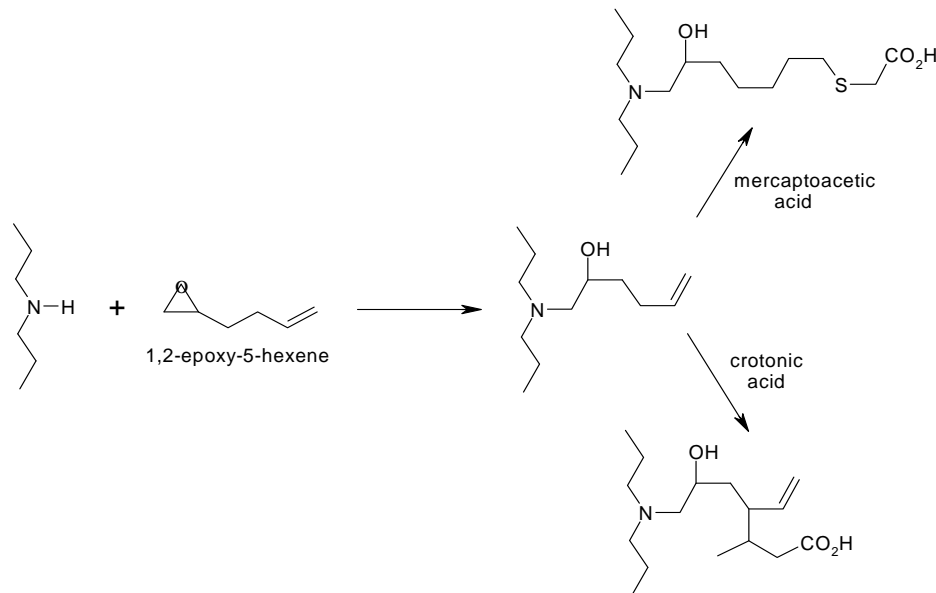
Siloxane type materials show an enhanced biostability over conventional PU, thus the above reaction will facilitate a PU with enhanced biostability.

B.G. Willoughby

Reactive Processing of PU (cont.)

- As mentioned earlier, device migration under normal loading is a serious issue with a spinal nucleus prosthetic.
- It was thought that an acid surface would bind the TPCU implant to the amine groups of the portentous material of the annulus fibrosis, thus anchoring the device in place.

1.



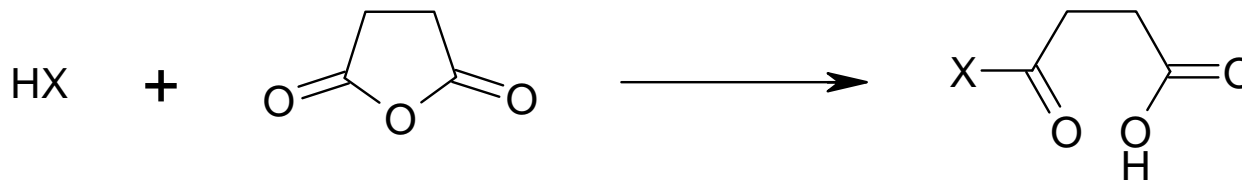
➤ The reaction involves the N-H of the PU therefore temperatures greater than the T_m of the hard segment are required.

➤ An epoxide ring opening reaction followed by either mercapto acetic acid or crotonic acid may facilitate an acid surface, as shown.

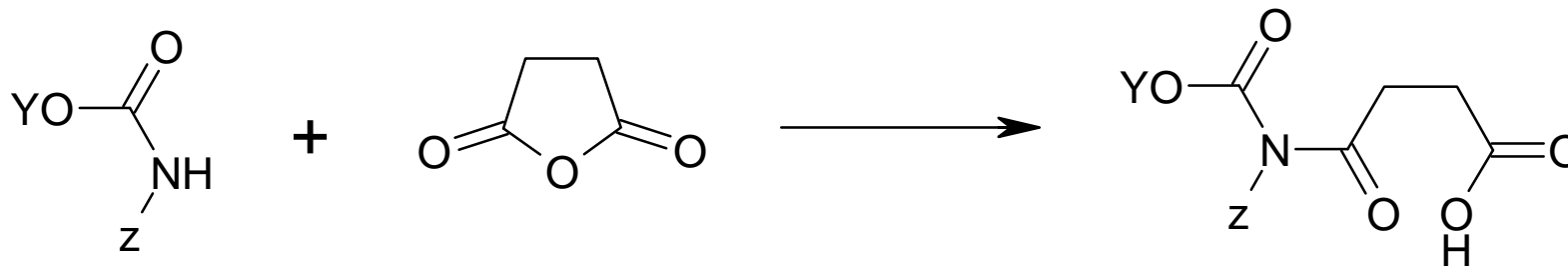
Reactive Processing of PU (cont.)

2. Anhydride Ring opening reaction.

The reaction of interest here is that of a cyclic anhydride, where ring opening by an active-hydrogen species (HX) gives a carboxylic acid pendant group.

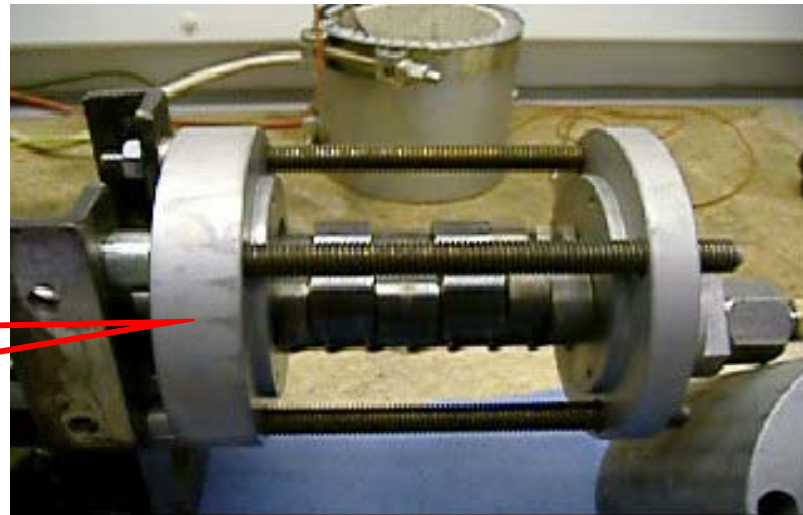


The reaction with a urethane N-H can be represented as follows:



Reactive Processing of PU (cont.)

- The Gale/ Smithers Rapra mini mixer was modified to facilitate a sealed reaction at PU melt temperatures, 180\leftrightarrow220°C.



Thermoplastic PCU synthesis

- An MDI-based polycarbonate Urethane was formulated in a two stage process targeting the previously mentioned mechanical properties required for a nucleus prosthetic device.

Stage 1.

A 3:1 pre-polymer (NCO:OH) was prepared by reacting MDI (Sigma Aldrich; used as received) with a mixture of two Mw oligomeric Hexamethylene carbonate diols; Mw 650 and Mw 2000 (Sigma Aldrich; dried under vacuum for 8 hrs) blended in a 1:1 ratio by equivalent weight.

MDI was placed in a reaction vessel under a dry nitrogen stream and held between 70-80°C. The polycarbonate diol mixture was added slowly over 40 minutes under stirring.

Stage 2.

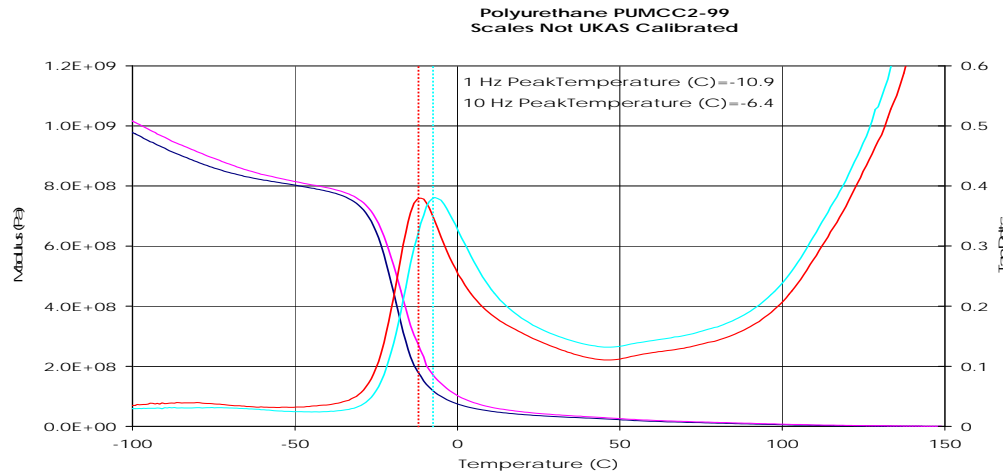
The pre-polymer was chain extended with Butane diol (Sigma-Aldrich, dried under vacuum for 8 hrs), yielding an overall stoichiometry of 1:1 NCO:OH, therefore yielding a thermoplastic PCU.

Results and Discussion: Sterilisation studies

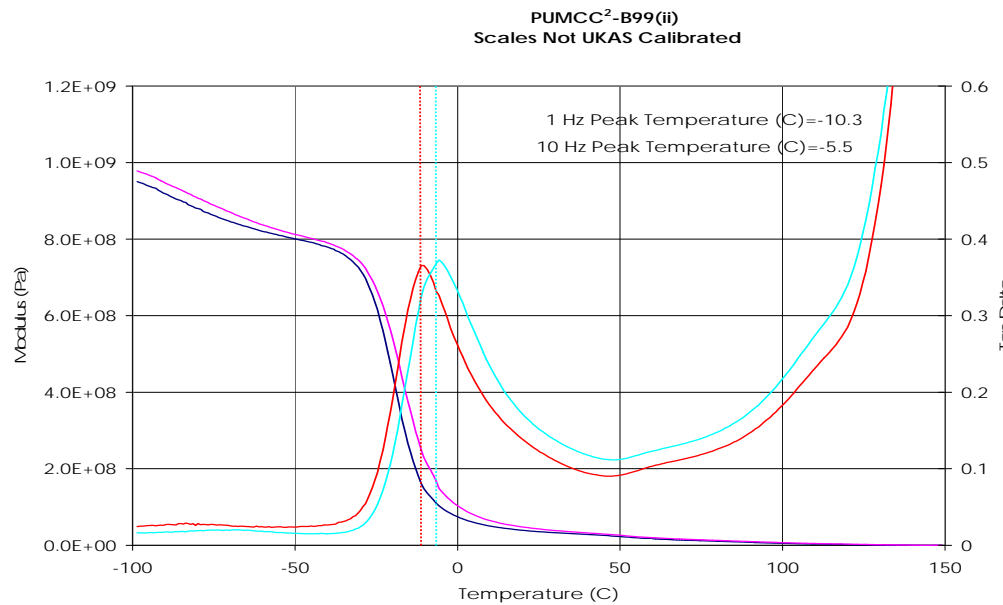
➤ The SRT TPCU was characterised pre and post electron beam sterilisation using the following techniques:

- DMTA: Thermal Events.
- FTIR: Functional Group.
- Mechanical Testing: Reduction in properties on sterilisation.
- GPC: Molecular weight Changes.

DMTA Pre- and Sterilised Sample



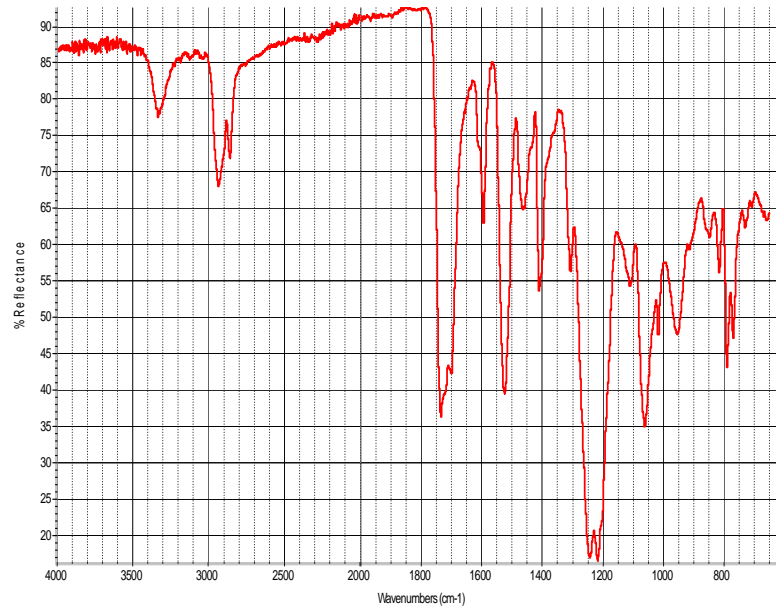
Pre-Sterilisation



e- beam sterilised.
25 kGy

FTIR-Golden Gate

JN0006-04.Via S Rowlands. Golden gate IR of fresh cut surface of PUMCCB-99 sample as received.HF
AV25743

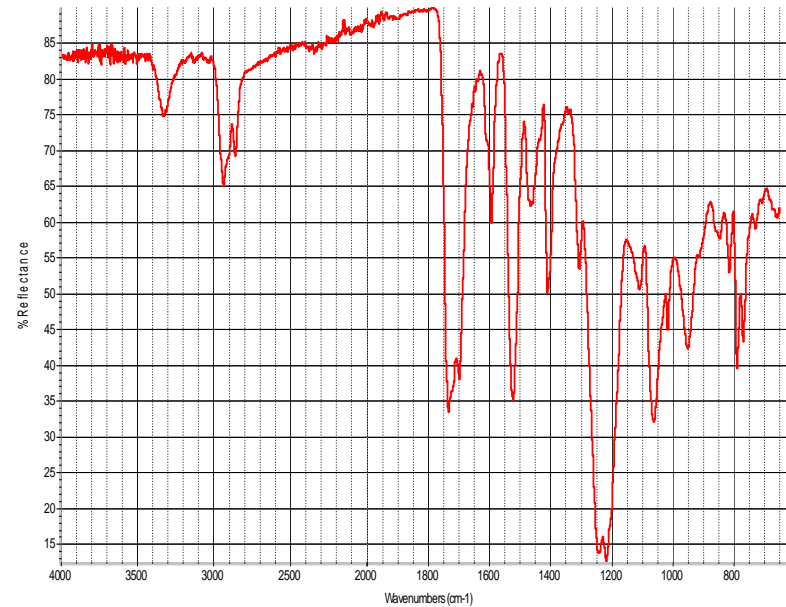


Smithers Rapra

Collection time: Thu Jun 11 12:25:37 2009

Pre-sterilisation

JN0006-04. Research Projects. Golden Gate IR of (1) PUMCC2 - B99(ii) fresh cut surface as received. BH.
AV25899



Smithers Rapra

Collection time: Thu Jul 02 08:36:13 2009

Post-Sterilisation

Mechanical Testing

Maximum Tensile Strength (MPa)

Sample	1	2	3	4	5	Median
Unsterilised PU	16.6	10.4	15.2	10.6	10.8	10.8
Sterilised PU	11.1	14.1	13.0	11.5	15.3	13.0

100% Modulus (MPa)

Sample	1	2	3	4	5	Median
Unsterilised PU	9.34	7.91	8.92	8.05	8.23	8.23
Sterilised PU	8.10	8.30	8.20	8.20	8.30	8.20

200% Modulus (MPa)

Sample	1	2	3	4	5	Median
Unsterilised PU	12.34	9.38	11.38	9.62	9.91	9.91
Sterilised PU	9.7	10.5	10.4	10.0	10.8	10.4

Mechanical Testing (cont.)

Tear Strength (N/mm)

Sample	1	2	3	Median
Unsterilised PU	61.2	59.0	60.8	60.8
Sterilised PU	61.2	59.8	61.8	61.2

Shore A Hardness (3 second)

Sample	1	2	3	4	5	Median
Unsterilised PU	89	80	90	90	91	90
Sterilised PU	91	89	89	90	91	90

Mechanical Testing (cont.)

Shore A Hardness (15 second)

Sample	1	2	3	4	5	Median
Unsterilised PU	90	90	90	90	90	90
Sterilised PU	90	88	89	89	90	89

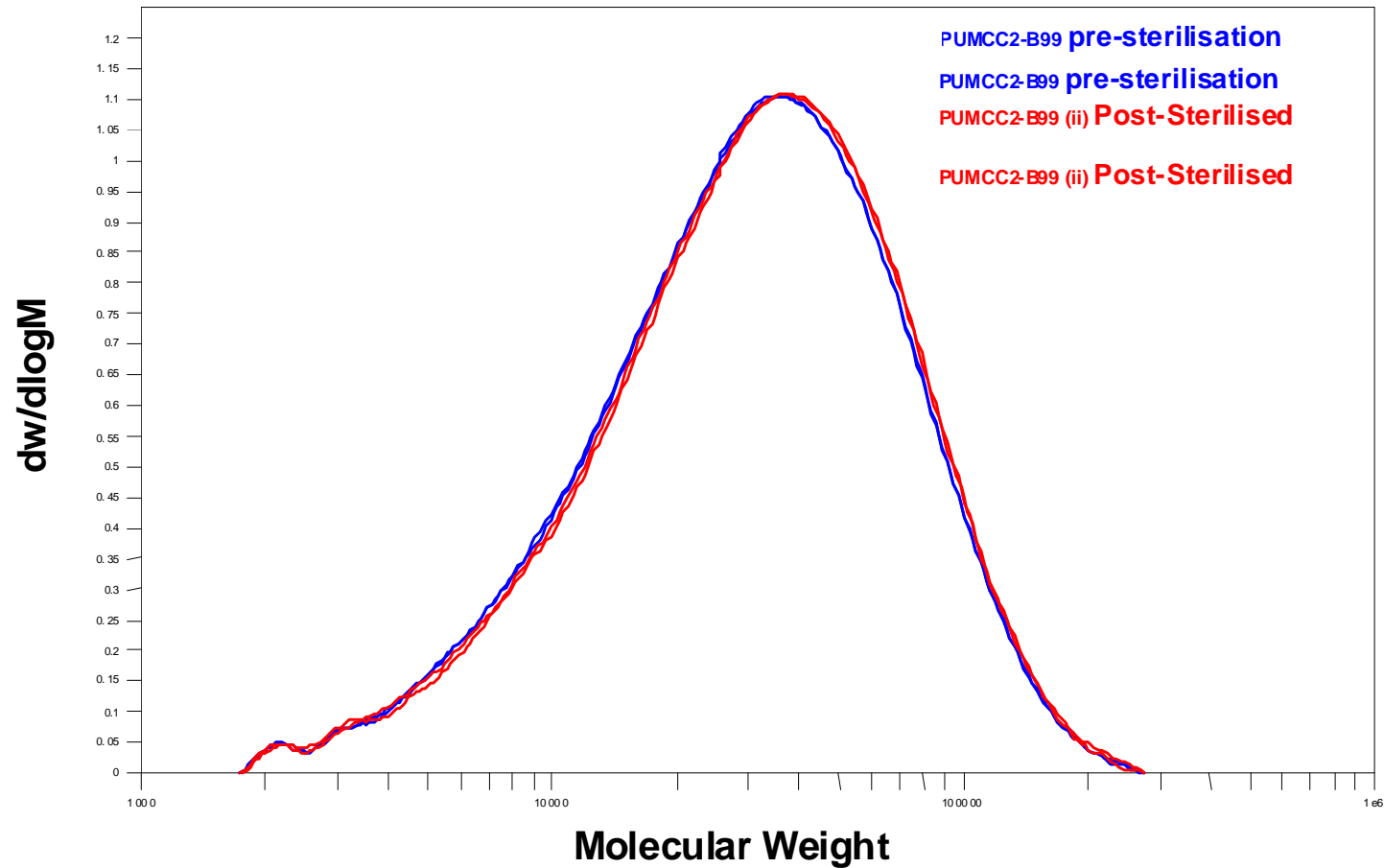
	Unsterilised PU	
Test No.	Compression Modulus @ 10% (MPa)	Compression Modulus @ 20% (MPa)
1	13.3	23.8
2	16.5	26.4
3	15.8	25.6
Mean	<u>15.2</u>	<u>25.3</u>

GPC: Chromatographic Conditions for PU Investigations

Instrument:	Polymer Laboratories PL-GPC 120 with PL-AS-MT auto sampler.	
Columns:	PL gel guard plus 2 x mixed-B, 30 cm, 10 μm ,	
Solvent:	N,N'-dimethyl formamide with 0.01M lithium bromide,	
Flow-rate:	1.0 mL/min (nominal),	
Temperature:	PL-GPC 120:	80°C (nominal),
	PL-AS-MT:	80°C (nominal),
Detector:	Refractive index.	
Standards:	PMMA.	

GPC Trace For Sterilised And Un Sterilised TPCU

MOLECULAR WEIGHT DISTRIBUTIONS



Summary

- An aromatic polycarbonate Urethane (PCU), of shore 90A hardness was prepared.
- The PCU was electron beam sterilised by Custom-IMD partner LasMed with a dosage of 25 kGy.
- The PCU was characterised pre- and post sterilisation in order to determine any detrimental effects of the sterilisation technique on the PCU.
- No significant changes were observed pre and post sterilisation.
- Therefore e-beam sterilisation is an appropriate sterilisation method for this type of material.

Summary

- Spinal prosthesis is technically challenging, PU used for its Bulk mechanical properties.
- Polycarbonate soft segment used for enhanced biostability.
- An aromatic polycarbonate Urethane (PCU), of shore 90A hardness was prepared.

Further Information

For further information on Custom IMD and the technical developments made within the project, you can access the project training materials, which are available on the Extended Services website. Please visit: www.customimd.eu and click on the link to the 'Extended Services' webpage.



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Contract No: 026599.



SIXTH FRAMEWORK PROGRAMME