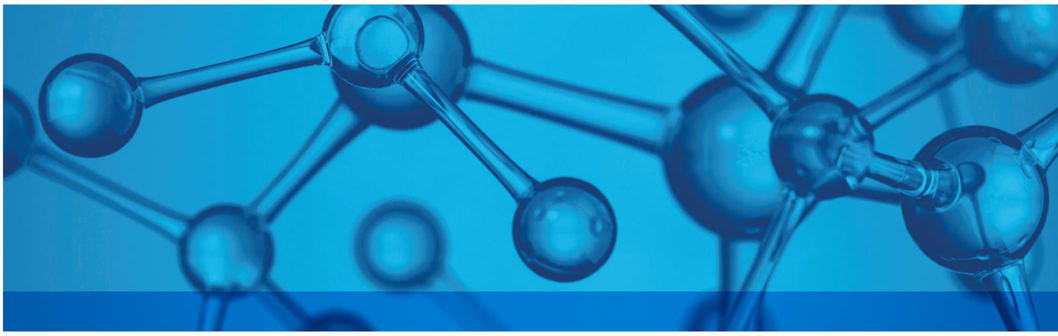

Shelf Life and Sterilization Study

KetaSpire® KT-880 NT

KetaSpire® polyetheretherketone (PEEK) is part of Solvay's family of Healthcare grade polymers, a line of high-performance polymers offered for use in medical devices and instruments, specifically those that are in contact with bodily tissue or fluids for less than 24 hours. KetaSpire® PEEK is available in high viscosity (KT-820) and low viscosity (KT-880) grades.

This document presents test results showing that KetaSpire® KT-880 NT is highly resistant to changes in mechanical, thermal and chemical properties after being exposed to gamma, steam, and ethylene oxide (ETO) sterilization. In addition, thermally accelerated aging studies spanning five years show that the calculated shelf-life of KetaSpire® KT-880 NT to be in excess of 100 years in closed ambient conditions.

Accelerated Aging Procedures

Test samples were prepared by injection molding KetaSpire® KT-880 NT from production lot YE-10026. Standard published injection molding parameters for KetaSpire® PEEK resin were used to prepare ASTM Type I tensile bars and ASTM flexural bars. Samples had a nominal 3.12 mm thickness and were not annealed prior to testing.

For both non-sterilized and gamma-sterilized testing, the control samples were stored in a climate-controlled lab environment kept at 23 °C and 50 % relative humidity. The accelerated aging test samples were placed inside a calibrated oven set to 100 °C with a constant air flow rate. Testing was performed at 12, 24, 36, 48 and 60-month intervals at Solvay's laboratories in Alpharetta, GA, which have ISO 9001 certification and A2LA ISO 17025 accreditation. Test method details are provided in the Equipment References section at the end of this document.

Gamma Sterilization

Samples were submitted to the Sterigenic's Facility in Haw River, NC for gamma sterilization, which was conducted using Sterigenic's procedures per requirements of the submitted packaging and material load.

Samples were irradiated in January 2012 under Work Order #784884, and were exposed to a minimum of 100 kGy accumulated dosage. After exposure, samples were returned to Solvay for property evaluation and inclusion in the standard and accelerated aging study.

Shelf Life and Gamma Sterilization Results

Standard and accelerated aging results with and without Gamma exposure are presented in the following tables. Tables 1 and 2 show results without Gamma sterilization and tables 3 and 4 show results with Gamma exposure.

Test results indicate that KetaSpire® KT-880 NT is highly resistant to significant changes in mechanical, thermal, and biological properties after exposure to aging and/or gamma sterilization. Samples maintained at 100 °C for five years observed a slight increase in strength and stiffness along with a slight decrease in ductility. Samples irradiated with gamma radiation displayed an initial slight color shift, which is typical for these types of polymers; even when combined with long term heat aging the color shift was still relatively minor.

Table 1: KetaSpire® KT-880 NT shelf life without gamma sterilization (aged at 23 °C, 50 % RH)

Property	Unit	As Molded	1 Year	2 Years	3 Years	4 Years	5 Years	Test Method
Color – CIE L*a*b								
Color change	ΔE	0.0	5.2	2.6	5.2	5.0	5.6	
Characteristic temperatures – DSC								ASTM D3418
Glass transition (T_g)	°C	148.7	147.9	148.0	147.0	148.4	147.2	
Recrystallization (T_c)	°C	295.6	295.8	295.3	295.4	296.8	296.6	
Melt temperature (T_m)	°C	341.6	343.7	341.9	341.0	343.6	343.0	
Tensile properties								ASTM D638
Strength at yield	MPa	100.7	102.0	100.0	99.3	100.1	101.4	
Elongation at yield	%	5.7	5.8	5.7	5.6	5.7	5.5	
Strength at break	MPa	74.5	68.2	68.9	66.2	66.7	66.9	
Elongation at break	%	15.4	20.0	16.0	19.0	20.0	19.0	
Modulus of elasticity	MPa	3,819	3,923	3,854	3,882	3,900	4,000	
Biocompatibility								
Cytotoxicity		Pass	Pass	Pass	Pass	Pass	Pass	ISO 10993:5
Physiochemical testing		Pass	Pass	Pass	Pass	Pass	Pass	ISO 10993:18

Table 2: KetaSpire® KT-880 NT shelf life without gamma sterilization (aged at 100 °C, ambient RH)

Property	Unit	As Molded	1 Year	2 Years	3 Years	4 Years	5 Years	Test Method
Color – CIE L*a*b								
Color change	ΔE	0.0	5.7	1.3	5.4	5.2	5.5	
Characteristic temperatures – DSC								ASTM D3418
Glass transition (T_g)	°C	148.7	147.7	149.3	148.8	148.5	148.0	
Recrystallization (T_c)	°C	295.6	296.0	298.9	297.1	296.5	295.9	
Melt temperature (T_m)	°C	341.6	343.3	343.1	341.6	342.9	343.1	
Tensile properties								ASTM D638
Strength at yield	MPa	100.7	104.1	106.2	106.2	107.0	105.6	
Elongation at yield	%	5.7	4.8	4.8	4.6	4.7	4.5	
Strength at break	MPa	74.5	75.1	68.2	68.1	69.0	68.0	
Elongation at break	%	15.4	15.0	16.0	20.0	27.0	16.0	
Modulus of elasticity	MPa	3,819	3,895	3,957	4,040	4,000	4,000	
Biocompatibility								
Cytotoxicity		Pass	Pass	Pass	Pass	Pass	Pass	ISO 10993:5
Physiochemical testing		Pass	Pass	Pass	Pass	Pass	Pass	ISO 10993:18

Table 3: KetaSpire® KT-880 NT shelf life with gamma sterilization (aged at 23 °C, 50 % RH)

Property	Unit	After Gamma	1 Year	2 Years	3 Years	4 Years	5 Years	Test Method
Color – CIE L*a*b								
Color change	ΔE	2.9	5.4	0.8	5.4	5.1	5.6	
Characteristic temperatures – DSC								ASTM D3418
Glass transition (T_g)	°C	148.8	148.2	148.4	147.8	147.4	146.6	
Recrystallization (T_c)	°C	295.3	295.6	295.0	294.8	296.9	297.0	
Melt temperature (T_m)	°C	342.2	345.5	342.0	328.8	343.2	342.5	
Tensile properties								ASTM D638
Strength at yield	MPa	103.4	102.0	103.4	103.4	102.1	101.4	
Elongation at yield	%	6.0	5.8	5.8	5.8	5.8	5.6	
Strength at break	MPa	68.6	68.5	67.8	68.7	67.0	67.7	
Elongation at break	%	17.4	25.0	16.0	26.0	27.0	18.0	
Modulus of elasticity	MPa	3,805	3,826	3,930	4,006	4,000	4,000	
Biocompatibility								
Cytotoxicity		Pass	Pass	Pass	Pass	Pass	Pass	ISO 10993:5
Physiochemical testing		Pass	Pass	Pass	Pass	Pass	Pass	ISO 10993:18

Table 4: KetaSpire® KT-880 NT shelf life with gamma sterilization (aged at 100 °C, ambient RH)

Property	Unit	After Gamma	1 Year	2 Years	3 Years	4 Years	5 Years	Test Method
Color – CIE L*a*b								
Color change	ΔE	2.9	6.7	4.3	4.3	7.2	7.3	
Characteristic temperatures – DSC								ASTM D3418
Glass transition (T_g)	°C	148.8	154.6	148.3	148.3	148.0	147.2	
Recrystallization (T_c)	°C	295.3	293.8	299.1	299.1	296.8	296.3	
Melt temperature (T_m)	°C	342.2	345.6	342.5	342.5	343.1	342.7	
Tensile properties								ASTM D638
Strength at yield	MPa	103.4	104.8	106.2	106.2	105.6	103.5	
Elongation at yield	%	6.0	4.9	4.8	4.8	4.8	4.5	
Strength at break	MPa	68.6	67.8	68.7	68.7	67.6	66.4	
Elongation at break	%	17.4	16.0	16.0	16.0	25.0	15.0	
Modulus of elasticity	MPa	3,805	3,909	3,985	3,985	3,900	4,000	
Biocompatibility								
Cytotoxicity		Pass	Pass	Pass	Pass	Pass	Pass	ISO 10993:5
Physiochemical testing		Pass	Pass	Pass	Pass	Pass	Pass	ISO 10993:18

Explanation of Biocompatibility Testing

Samples submitted for biocompatibility testing were tested by NAMSA laboratories using appropriate protocols for ISO 10993:5 and 10993:18. The ISO 10993:18 testing was conducted with two extracts: sodium chloride (NaCl) and hexane. Cytotoxicity and physiochemical testing results are summarized in Table 5.

Table 5: KetaSpire® KT-880 NT biocompatibility testing acceptance criteria

Property	Unit
Cytotoxicity	
Cell reactivity	Grade 0 – no cell lysis
Physiochemical testing – aqueous NaCl	
Non-volatile residue	≤ 1 mg
Residue on ignition	≤ 1 mg
Heavy metals	≤ 1 ppm
Buffering capacity	≤ 1.0 ml
Physiochemical testing – Hexane	
Non-volatile residue	≤ 1 mg
Residue on ignition	< 1 mg
Turbidity	≤ 0.6 NTU

Thermal Aging

Thermal aging was used to accelerate the shelf-life aging study of KetaSpire® KT-880 NT. There are multiple approaches commonly used with plastics to estimate the equivalency of accelerated thermal aging.

Method 1: Every 10 °C Doubles the Rate

A standard rule in the plastics industry, outlined by Hukins et al. (2008), is that increasing the temperature by 10 °C doubles the rate of aging, as illustrated by Equation 1, where f is the accelerated aging factor.

Equation 1: $$f = 2^{\frac{\Delta T}{10}}$$

KetaSpire® KT-880 NT underwent a five-year aging study at 23 °C and 100 °C. At the five-year mark, all test results indicate that there is no measurable thermal decomposition. Plugging $\Delta T = 100 - 23 = 77$ °C into Equation 1 estimates that KetaSpire® KT-880 NT aging at 100 °C for five years is equivalent to 23 °C for 1,040 years.

Method 2: Arrhenius' Equation

The Arrhenius' equation (Equation 2) is commonly used to estimate the acceleration factor caused by thermal-oxidative accelerated aging, where k is the chemical reaction rate, A is the pre-factor, E_a is the activation energy, R is the universal gas constant, and T is the absolute temperature.

Equation 2: $$k = Ae^{-\frac{E_a}{RT}}$$

A modification of Arrhenius' equation (Equation 3) can be used to estimate the increase in reaction rate brought about by an increase in temperature, where k_2/k_1 is the acceleration factor brought about by the increase in temperature from T_1 to T_2.

Equation 3: $$\frac{k_2}{k_1} = \frac{Ae^{-\frac{E_a}{RT_2}}}{Ae^{-\frac{E_a}{RT_1}}} = e^{-\frac{E_a}{R} \times \left(\frac{1}{T_2} - \frac{1}{T_1}\right)}$$

This simplification assumes that the pre-exponential factors for each temperature are approximately equivalent when both temperatures fall within the same phase. In order to solve for k_2/k_1, an activation energy must be determined for thermal-oxidative decomposition observed as a result of the accelerated aging.

However, this poses a problem for KetaSpire® KT-880 NT due to no significant thermal decomposition occurring at 23 °C or 100 °C after 5 years. Theoretically, no thermal decomposition corresponds to infinite activation energy. An alternative conclusion is that the rate of decomposition is too slow to be measurable. As PEEK is among the most thermally stable polymers, it is reasonable to assume that high activation energy is required to decompose it.

For example, Kang et al. (2006) estimated a thermal decomposing activation energy for PEEK of 241.87 kJ/mol. Using this activation energy in Equation 3 with a T_1= 23 °C and T_2 = 100 °C estimates that 100 °C for 2 years is equivalent to 23 °C for approximately 954 million years. Even assuming a very small activation energy, such as an E_a = 85 kJ/mol at 100 °C of low density polyethylene (LDPE), Ding et al (1999) estimates that 100 °C for 5 years is equivalent to 23 °C for 6,245 years.

In conclusion, KetaSpire® PEEK is very thermally stable, showing no signs of degradation at both 23 °C and 100 °C over 5 years. Conservative use of the standard plastic industry rules for accelerated aging or Arrhenius' equation estimates that 5 years of 100 °C accelerated thermal aging performed on KetaSpire® KT-880 NT is equivalent to 1,000+ years at 23 °C.

Steam Sterilization

KetaSpire® KT-880 NT samples were exposed continuously in a Pre-Vac sterilizer for 500 cycles using the following conditions:

- Unit: Amsco Century Sterilizer SV-136H
- Cycle: Pre-Vac
- Temperature: 134 to 136 °C
- Pressure: 35 to 37 psig
- Vacuum: 27 in. Hg
- Sterilization Times: 18 minutes sterilization, 10 min drying, 36 minutes total cycle

The unit uses a dedicated steam generator supplied by filtered, deionized water, which is chemically balanced per the sterilizer unit manufacturer's recommendations. Testing method details are provided in the equipment references section of this document. Relative results of the effects of 500 cycles of steam sterilization on KetaSpire® KT-880 NT are presented in Table 6.

Test results indicate that KetaSpire® KT-880 is capable of resisting significant mechanical, thermal, and biological changes as a result of extensive steam sterilization. A slight increase in strength and stiffness along with a slight decrease in elongation was believed to be caused by stress relaxations occurring within the amorphous phase at elevated temperatures. The observed color shift was small. Please refer to the Explanation of Color Change section in this document for a description of ΔE values. While slight changes were observed in other testing conditions, they were all within the confines of expected testing error. With no significant changes occurring as a result of aging or steam sterilization, it is believed that devices composed of KetaSpire® KT-880 NT can be exposed to both a long shelf life and repeated cycles of steam sterilization without significantly affecting mechanical, thermal, or biological properties.

Table 6: KetaSpire® KT-880 steam sterilization results

Property	Unit	As molded	1 Year	Test Method
Color – CIE L*a*b				
Color change	ΔE	0.0	3.1	
Characteristic temperatures – DSC				ASTM D3418
Glass transition (T_g)	°C	148.7	149.1	
Recrystallization (T_c)	°C	295.6	295.4	
Melt temperature (T_m)	°C	341.6	342.5	
Tensile properties				ASTM D638
Strength at yield	MPa	100.7	108.9	
Elongation at yield	%	5.7	4.5	
Strength at break	MPa	74.5	68.8	
Elongation at break	%	15.4	11.1	
Modulus of elasticity	MPa	3,819	3,964	
Biocompatibility				
Cytotoxicity		Pass	Pass	ISO 10993:5
Physiochemical testing		Pass	Pass	ISO 10993:18

Ethylene Oxide (ETO) Sterilization

KetaSpire® KT-880 NT samples for ETO sterilization were submitted to the Sterigenics Facility in Willowbrook, IL for ETO sterilization. Sterilization was conducted using Sterigenics procedures per requirements of the submitted packaging and material load. Sterilization was conducted in January 2012 using Sterigenics EO Cycle #21 exposure conditions.

Samples were then returned to Solvay for property evaluations and documentation. Details of testing methods utilized are provided in the Equipment References section of this document. Relative results of KetaSpire® KT-880 NT exposed to 5 cycles of ETO sterilization are presented in Table 7.

Test results indicate that KetaSpire® KT-880 NT is resistant to mechanical, thermal, and chemical changes after ETO sterilization. While slight changes were observed in some testing conditions all were within the confines of expected testing error. With no significant changes resulting from aging or ETO sterilization, it is believed that samples can be stored for an indefinite time after exposure to ETO sterilization without any adverse effects on properties.

Table 7: KetaSpire® KT-880 ETO sterilization results

Property	Unit	As Molded	500 Cycles	Test Method
Color – CIE L*a*b				
Color change	ΔE	0.0	1.2	
Characteristic temperatures				ASTM D3418
Glass transition (T_g)	°C	148.7	148.4	
Recrystallization (T_c)	°C	295.6	297.7	
Melt temperature (T_m)	°C	341.6	343.3	
Tensile properties				ASTM D638
Strength at yield	MPa	100.7	98.6	
Elongation at yield	%	5.7	5.6	
Strength at break	MPa	74.5	66.2	
Elongation at break	%	15.4	14.3	
Modulus of elasticity	MPa	3,819	3,847	
Biocompatibility				
Cytotoxicity		Pass	Pass	ISO 10993:5
Physiochemical testing		Pass	Pass	ISO 10993:18

Explanation of Color Change

LAB color space was used for evaluation of color change. Color space is tracked using three values: L (brightness), a (red/green), and b (blue/yellow), representing a three-dimensional color space. A single numerical value, ΔE, can be used to estimate the degree of overall color change using Equation 4. Color changes as seen by the naked eye are summarized in Table 8.

Equation 4: $$\Delta E = \sqrt{(L_2 - L_1)^2 + (a_2 - a_1)^2 + (b_2 - b_1)^2}$$

Table 8: Typical ΔE significance to the naked eye

ΔE Value	Color change as seen by the naked eye
$\Delta E < 1$	Unable to distinguish
$1 \leq \Delta E < 2$	Noticeable by some upon a close inspection
$2 \leq \Delta E < 3$	Noticeable upon inspection
$\Delta E \geq 3$	Obvious change in color

Equipment References

Tensile testing was conducted on an Instron® 5569 Load Frame at 2 in/min test speed per the ASTM D638 standard.

Thermal properties were tested using a TA Instruments® Q20 Differential Scanning Calorimeter per ASTM D3418 standard. Analysis used 1^{st} and 2^{nd} heat with a 20 °C/min ramp rate.

Color Change was measured on the wide end of a Type I tensile bar using a BYK Gardner® Colorsphere Instrument; Reflectance mode, CIE L*a*b* scale with a D65 – 10° illuminant and observer.

Cytotoxicity (ISO 10993-5) and Physio-Chemical analysis (ISO 10993-18) were conducted by the NAMSA laboratories in Northwood, OH.

Literature References

D. W. L. Hukins, et al., "Accelerated Aging for Testing Polymeric Biomaterials and Medical Devices," Med. Eng. & Phy., Vol. 30, pp. 1270–1274, 2008.

S. Ding, et al., "Polymer Durability Estimates Based on Apparent Activation Energies for Thermal Oxidative Degradation," Therm. Acta, 367–368, pp. 107–112, Apr. 2000.

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SpecialtyPolymers.EMEA@solvay.com | Europe, Middle East and Africa
SpecialtyPolymers.Americas@solvay.com | Americas
SpecialtyPolymers.Asia@solvay.com | Asia Pacific

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