Vivacit-E® Vitamin E Highly Crosslinked Polyethylene Long-term Performance For High Demand Patients

Background

Total joint replacement is being performed on younger patients who expect to remain active throughout their lifetime, and as such this demographic shift has created a need for long-term implant bearing performance.[1,64] First introduced in the 1990s, highly crosslinked polyethylene (HXPE) has demonstrated promising wear properties through the first decade of *in vivo* use.[2] Recent studies, however, have shown the potential for *in vivo* oxidation, which can affect long-term performance;[3-7] performance in the second and third decades of use is not known. After years of research and development, Zimmer has addressed the issue of *in vivo* oxidation with a proprietary method of grafting (locking) Vitamin E to HXPE that prevents oxidation.[8-19,44] The result is *Vivacit-E*® Vitamin E Highly Crosslinked Polyethylene, a bearing surface that delivers on the three critical performance characteristics of polyethylene:

1. **Exceptional oxidative stability[8,39-40]**
2. **Ultra-low wear[9-11,44]**
3. **Improved strength[12-13,43,60]**

Methods

Using traditional material/development strategies based on processing, microstructure and property relationships, Zimmer determined that an antioxidant-stabilized polyethylene could deliver long-term performance.[8-13,44] After significant research, Zimmer selected the antioxidant Vitamin E and developed a process that results in exceptional oxidative stability, ultra-low wear and improved mechanical strength.[8-13,44] An optimal quantity of Vitamin E is blended into the polyethylene powder to achieve a tightly controlled, homogeneous concentration throughout the material. Warm e-beam irradiation is then applied to Vitamin E polyethylene blocks with an effective irradiation dose comparable to the clinically proven *Longevity*® HXPE (e.g. 10 MRad).[2] The irradiation process forms crosslinks resulting in ultra-low wear, while also grafting or locking the Vitamin E directly to the polyethylene chain for long-lasting oxidative stability.[8-11, 14-19,43,44] Since the Vitamin E in the polyethylene actively and continuously prevents oxidation, the presence of Vitamin E eliminates the need for post-irradiation remelting, resulting in improved mechanical strength.[12-13,60]

Performance

Vivacit-E® HXPE underwent extensive in-vitro testing to prove the long-term performance advantages over the current best-in-class materials. Both remelted HXPE and gamma-irradiated conventional polyethylene (CPE) failed prior to ten weeks of accelerated aging.[8,43] In contrast, *Vivacit-E* HXPE prevented oxidation and maintained mechanical properties after 33 weeks of accelerated aging; a test which lasted more than 16 times longer than the industry standard.[8,46,55] In-vitro wear testing on a hip simulator proved that *Vivacit-E* HXPE exhibits a 94% reduction in overall wear vs. CPE, as well as comparable wear to *Longevity* HXPE after an unprecedented 75 million cycles.[9-11,44] Through in-vitro knee simulator testing, the *Vivacit-E* HXPE material also exhibited 90% and 96% reduction in unicompartmental and total knee arthroplasty applications, respectively, compared to conventional predicate designs.[58] Furthermore, at least 36x greater resistance to delamination was exhibited compared to conventional polyethylene.[59] Mechanical testing also proved that *Vivacit-E* HXPE maintains and even improves upon the strength of gamma-irradiated conventional polyethylene, which is an improvement in the strength of HXPE.[12,13] This was further proven through in-vitro spine fatigue testing of a posterior-stabilized (PS) articular surface, where a 10% improvement of the fatigue strength of the spine was exhibited.[60]

Competitive Comparison

In comparative testing, *Vivacit-E* HXPE outperformed both Biomet E1 and Stryker X3. Biomet E1, an antioxidant HXPE where the polyethylene is soaked in Vitamin E, exhibited a non-uniform distribution of Vitamin E throughout the components, with less Vitamin E at the articulating surface compared to the backside. *Vivacit-E* HXPE maintained a tightly-controlled, homogeneous concentration of Vitamin E throughout the components from articulating surface to backside.[27] Furthermore, high levels of grafting of the Vitamin E to the polyethylene does not occur when the polyethylene is soaked in Vitamin E, which can result in the elution of Vitamin E from the material.[27,67] Stryker X3, a sequentially annealed HXPE. was compared to *Vivacit-E* HXPE in terms of strength, oxidation and wear. Accelerated aging of Stryker X3 for up to four weeks resulted in up to a 68% loss in mechanical strength, while *Vivacit-E* HXPE retained its mechanical strength after accelerated aging for more than eight times

longer than the Stryker X3.[46] In-vitro knee wear simulator testing demonstrated a 39.6% reduction in wear of *Vivacit-E* HXPE compared to Stryker X3. Furthermore, after 5.0 million cycles of wear testing, Stryker X3 exhibited a significant increase in oxidation as well as "white banding."[65] In-vitro testing is bolstered by retrieval studies of annealed HXPEs, including Stryker X3, which showed high levels of oxidation after 7.1 years *in vivo*.[4,47]

Conclusions

The increased utilization of total joint arthroplasty on a younger patient population has challenged the orthopaedic industry to develop implants designed for long-term performance. *Vivacit-E* HXPE is designed to meet the long-term performance needs of the most demanding patients by grafting or locking the Vitamin E directly to highly crosslinked polyethylene. The result is a polyethylene articulating surface material that delivers exceptional oxidative stability, ultra-low wear and improved mechanical strength for long-term *in vivo* performance.[8-13,44]

Introduction

Younger and More Demanding Patient Population

Joint replacement is occurring in increasingly younger patients (Figures 1 and 2).[1] Over one-fifth of primary total hip arthroplasty (THA) procedures in the United States occur in patients 55 years of age or younger.[1] Between 2000 and 2009, the number of total knee arthroplasty (TKA) procedures performed increased by 188% among patients who were 45-64 years old.[64] This younger patient population expects to remain active throughout their lives, creating a need for longer-lasting and higher-performance implants.

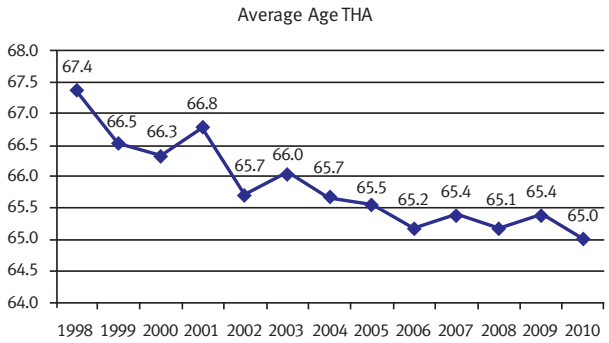


Figure 1. Total hip replacement average patient age in US.[1]

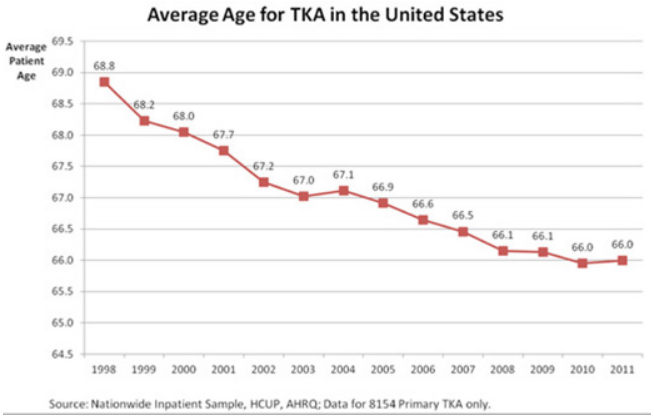


Figure 2. Total Knee replacement average patient age in US.[1]

Highly Crosslinked Polyethylene Utilization on High Demand Patients

The decline of metal-on-metal (MoM) use in hips has prompted many surgeons to utilize highly crosslinked polyethylene (HXPE) with ceramic heads for high demand patients.[66] HXPE was developed in the 1990s to reduce polyethylene wear and subsequent osteolysis that impacted clinical performance in previous generations of conventional polyethylene. A six center study led by Massachusetts General Hospital indicated that Zimmer's *Longevity* and *Durasul*® remelted highly crosslinked polyethylene hip implants have worked as predicted, with ultra-low *in vivo* wear at 12 years follow up.[2] These low wear rates in HXPEs provide confidence to surgeons utilizing larger diameter 36mm and 40mm articulations, which improve joint stability and reduce dislocation risks.[21-24]

In TKA, the introduction of HXPE in the early 2000s has led to a decrease in polyethylene wear for most patients.[61] In first-time revision TKAs performed between 2001 and 2011 at one institution, it was found that infection (24%) was a leading cause in the revision surgery. However, Kim, et al. found that polyethylene wear is one of the most common causes for revision in patients under the age of 55.[62] There are many failure modes that pertain to wear: burnishing, abrasion, scratching, third body, surface deformation and delamination, which is fatigue wear.[63] Despite improvements in wear and delamination with the introduction of HXPE, surgeons have been slower to adopt this material in the knee due a slight reduction in mechanical strength that is a consequence of crosslinking/remelting.[25]

Furthermore, the clinical success of HXPE has been tempered by recent studies showing oxidation in explanted articular surfaces.[3,4,52-54] Oxidation is a primary mechanism of aging in polyethylene that leads to an increase in wear and a decrease in overall strength of the components.[3-7,52-54] Two potential causes of *in vivo* oxidation are the absorption of readily oxidizing lipids

and the creation of free radicals during cyclic loading experienced during activities of daily living.[48] Retrieval studies are also showing that articular surfaces in the knee have higher rates of oxidation *in vivo* compared to acetabular liners in the hip.[52,53] It is not known if the reported oxidation and higher *in vivo* wear will impact clinical performance after longer periods *in vivo*, but the data from the retrieval studies suggests a need to reevaluate bearing technologies for younger more active patients seeking performance well beyond the first decade.

Vivacit-E Vitamin E HXPE, a Solution for High Demand Patients

To meet the need for longer-lasting implants, Zimmer engineered a new antioxidant stabilized HXPE – *Vivacit-E* Highly Crosslinked Polyethylene. *Vivacit-E* HXPE addresses oxidation through a proprietary process that grafts or locks the antioxidant Vitamin E to highly crosslinked polyethylene.[14-19] The result is a bearing material that delivers on the three characteristics required for long-term polyethylene performance: exceptional oxidative stability, ultra-low wear and improved mechanical strength (Figure 3).[8-13]

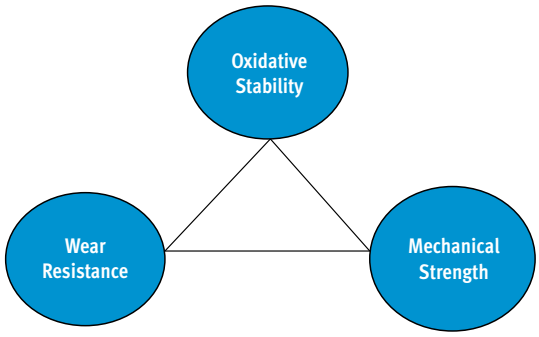


Figure 3. Important performance criteria of polyethylene.

This paper details the research Zimmer performed to develop *Vivacit-E* HXPE and determine its long-term performance advantages over current best-in-class materials.

Foundation of Antioxidant-Stabilized Polyethylene

Oxidative stability is one of the primary drivers of polyethylene's long-term clinical performance.[3-7] Irreversible and progressive oxidation occurs when free radicals, created during the irradiation crosslinking or *in vivo* cyclic loading during activities of daily living, come in contact with oxygen.[48] This oxidation process results in decreased mechanical properties and an increase in wear.[8,9] In order to prevent oxidation, free radicals must be quenched before they can react with oxygen.[25] This is the role of an antioxidant.

Selecting the Right Antioxidant

Zimmer researched and evaluated over 30 different antioxidants based on their ability to prevent oxidation, manufacturability and biocompatibility.[49] Vitamin E was selected for its strong antioxidant properties. As a dietary supplement, the human body naturally utilizes Vitamin E to protect cell membranes from oxidation.[25] Zimmer uses d/l alpha tocopherol, a high purity synthetic Vitamin E commonly used in dietary supplements, fortified foods and cosmetic products.

How Vitamin E Works

The antioxidant activity of Vitamin E (alpha-tocopherol) is created by hydrogen donation from the hydroxyl (OH) group on the chroman ring to a free radical on the polyethylene chain as shown in Figure 4.[25]

When Vitamin E is incorporated into the polyethylene, it continuously quenches free radicals so that they do not react with oxygen. This prevents the oxidation cycle and the subsequent degradation of polyethylene. A critical amount of Vitamin E is required to continuously prevent polyethylene oxidation.[25]

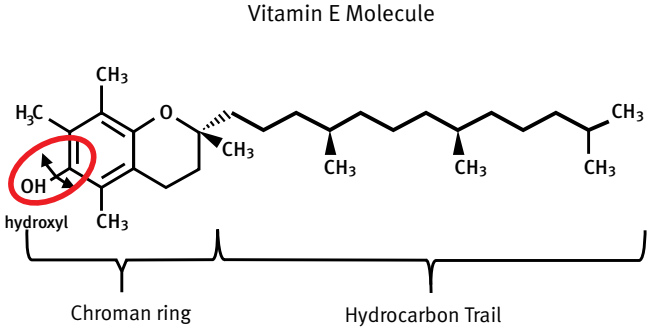


Figure 4. Molecular Structure of Vitamin E.

Processing Vitamin E Polyethylene for Optimized Performance

Vivacit-E HXPE Manufacturing Process

After significant research and consideration of different processes to add Vitamin E to polyethylene, Zimmer pursued a proprietary blending process designed to maximize oxidative stability, minimize wear and improve mechanical properties compared to traditional polyethylene (Figure 5). Vitamin E is blended directly into the polyethylene powder in order to achieve a tightly controlled, homogenous mixture of Vitamin E throughout the polyethylene. Warm e-beam irradiation is then applied with an effective dose comparable to that of a 10 MRad HXPE.[2] The irradiation grafts Vitamin E directly to the polyethylene chain for long-lasting oxidative stability and forms crosslinks which results in ultra-low wear properties.[9-11,14-19] The presence of Vitamin E in the polyethylene has the added benefit of eliminating the need to remelt the material after crosslinking to achieve oxidative stability, which results in improved mechanical strength.[12,13]

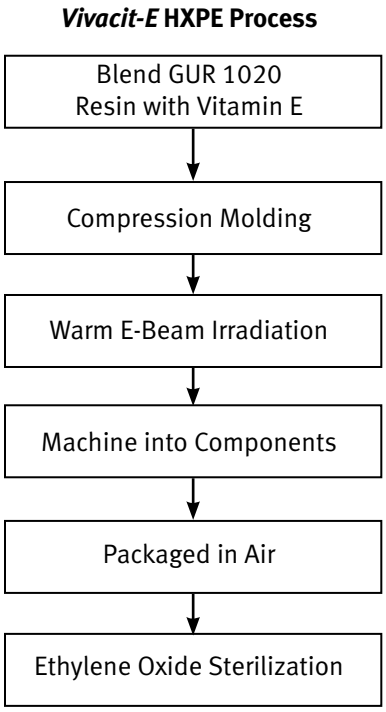


Figure 5. *Vivacit-E* HXPE manufacturing process.

Grafting: Bonding of Vitamin E to Polyethylene

Zimmer's proprietary process efficiently grafts greater than 90% of the Vitamin E to the polyethylene chain with covalent bonds, the chemical link of two atoms through the sharing of electrons.[19] This high level of grafting ensures that the optimal concentration of the antioxidant will be retained in the material to prevent oxidation.[18,19]

Grafting Prevents Vitamin E Elution for Long-Term Prevention of Oxidative Aging

To prove that grafting prevents elution of Vitamin E, aggressive extraction testing was performed to purposefully attempt to remove the Vitamin E using both polar and non-polar solvents. Even under these extreme extraction methods, well beyond *in vivo* conditions, the extract contained no Vitamin E (Figure 6), which proves that Vitamin E is retained in *Vivacit-E* HXPE.[41]

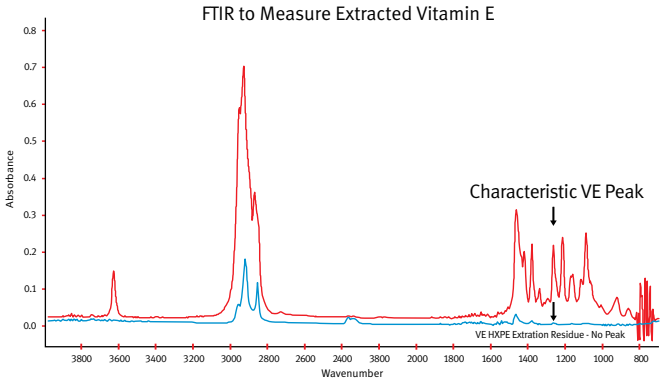


Figure 6. FTIR spectrum for hexane doped with neat Vitamin E (top) and hexane residue after attempted extraction of 0.30 wt%. Vitamin E HXPE sample (bottom). The arrow indicates the characteristic Vitamin E peak produced by the neat Vitamin E in hexane. The hexane residue from the Vitamin E HXPE sample does not exhibit a peak, showing that Vitamin E was not extracted from the samples.[41]

Exceptional Oxidative Stability

Vivacit-E HXPE Prevents Oxidation and Maintains Performance Properties After Extended Accelerated Aging

The exceptional oxidative stability of *Vivacit-E* HXPE was proven through aggressive accelerated aging tests.[8] As previously mentioned, oxidation is a primary mechanism of aging of polyethylene that results in decreased mechanical properties and increased wear.[25] The industry standard for accelerated aging, American Society for Testing and Materials (ASTM) F2003, specifies subjecting the polyethylene to elevated temperatures in a pure oxygen environment for two weeks. The intent is to force oxygen into the material and induce oxidation. *Vivacit-E* HXPE was subjected to this accelerated aging method for 16.5 weeks longer than the two week standard.[8]

Tensile testing measures the stress where a material undergoes critical deformation and the tension force at which the material fails. Figure 7 shows the percent retention of tensile strength for unaged and aged samples of *Vivacit-E* HXPE, remelted HXPE, and gamma-irradiated conventional polyethylene (CPE). Gamma-irradiated conventional polyethylene dramatically decreases in tensile strength after four weeks of accelerated aging. As expected, there is a significant delay in mechanical property degradation of the remelted polyethylene. *Vivacit-E* HXPE exhibits a negligible decrease in tensile strength after 24 weeks of extended accelerated aging and no measurable oxidation. Even after 33 weeks of aging, the *Vivacit-E* HXPE exhibited negligible change in strength and oxidation,[55] demonstrating that the Vitamin E in *Vivacit-E* HXPE actively and continuously prevents oxidation during extreme oxidative conditions.[8, 55]

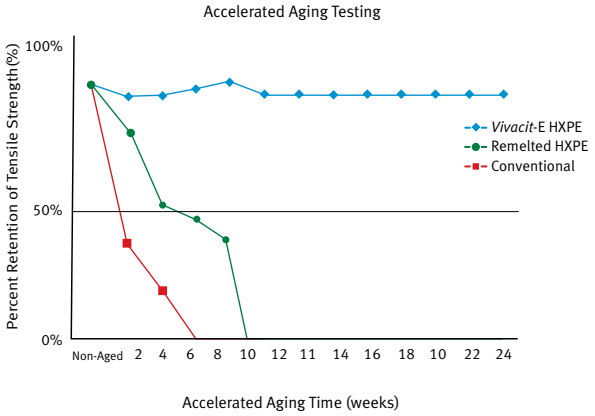


Figure 7. Retention of tensile strength at each aging interval per material.[8]

Resistance to Cracking Under Cyclic Stress in Oxidative Environment

In vivo oxidation may occur due to mechanical and/or cyclic loading which can lead to fracturing of the polyethylene.[39] In order to evaluate resistance to environmental stress cracking, CPE, remelted HXPE and *Vivacit-E* HXPE materials were subjected to a bending stress of 10 MPa at a frequency of 0.5 Hz in air at 80°C. CPE and remelted HXPE oxidized and cracked prior to completion of the 1.5 million cycle (Mc) test. In contrast, *Vivacit-E* HXPE did not crack and exhibited negligible oxidation for the prescribed 1.5 Mc of testing as shown in Figure 8.[40]

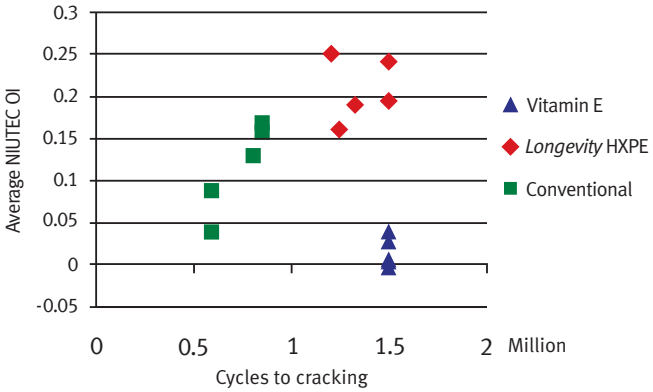


Figure 8. Average oxidative index versus cycles to cracking (arrows indicate no cracks at test endpoint) during cyclic loading of 10MPa at 0.5Hz in air at 80°C.[40]

Prevents Oxidation-Inducing Lipid Absorption

Highly crosslinked polyethylenes were developed to maintain long-term oxidative stability on the shelf and *in vivo*. Recent retrieval studies show signs of oxidation in HXPE materials that were originally thought to be stabilized long-term.[3-6] This unexpected phenomenon is likely due to *in vivo* oxidation of absorbed lipids or free radicals generated during cyclic loading. Lipids readily enter into oxidation reactions when they come in contact with free radicals. Therefore, there is a need to understand polyethylene lipid absorption.

Vivacit-E HXPE absorbs significantly less lipid fluid than either CPE or remelted HXPE. In a study comparing the fluid absorption properties of *Vivacit-E* HXPE to remelted HXPE, it was determined that *Vivacit-E* HXPE absorbed 50-88% less fluid than remelted HXPE after 45 Mc of in vitro wear testing of 40mm acetabular liners, as is shown in Figure 9.[56] The exact mechanism by which Vitamin E reduces fluid absorption is not well understood; however, it is most likely due to Vitamin E occupying free volume in the polyethylene which in turn reduces the space that can be occupied by lipids. Since the Vitamin E in *Vivacit-E* HXPE is grafted directly to the polymer chain after irradiation, it is resistant to displacement by lipids.[18-19, 56]

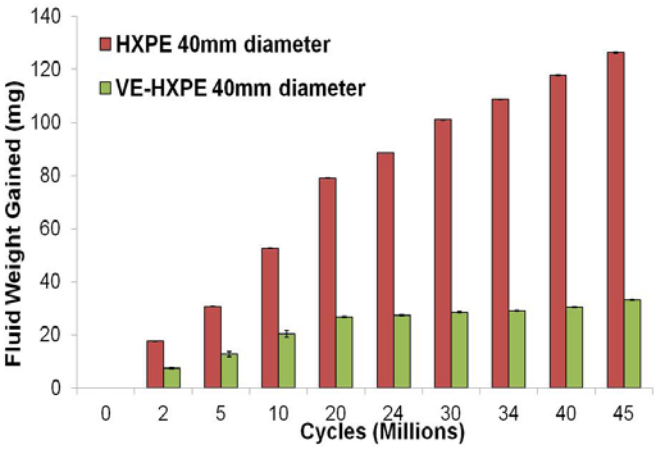


Figure 9. Fluid absorption by remelted HXPE and *Vivacit-E* HXPE during a 45Mc in-vitro wear test.[56]

Regarding oxidation due to lipid absorption, Figure 10 shows this effect for CPE, remelted HXPE and *Vivacit-E* HXPE as a function of time. Each material underwent accelerated aging followed by in vitro wear testing which is conducted in a lipid environment, followed by a second accelerated aging cycle. Absorption of readily oxidizing lipids during wear testing made the remelted HXPE and gamma-irradiated conventional polyethylene susceptible to oxidation during the second accelerated aging cycle. However, after 45 Mc of in vitro wear testing, followed by three rounds of additional accelerated aging, *Vivacit-E* HXPE exhibited no oxidation (oxidation indices ‹0.02).

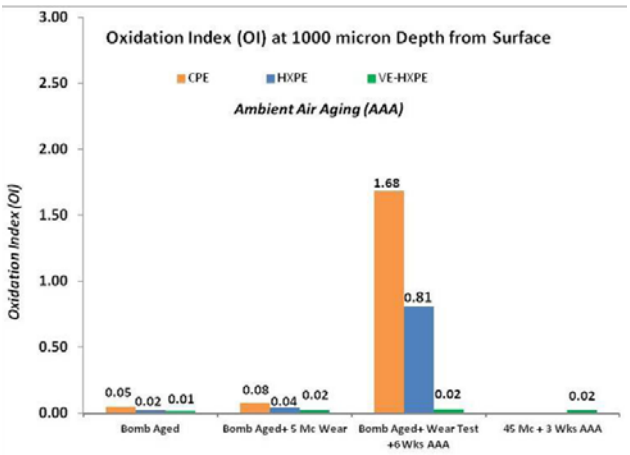


Figure 10. Comparison of gamma-irradiated conventional polyethylene, remelted HXPE and *Vivacit-E* HXPE oxidative index after accelerated aging, wear simulator testing followed by additional ambient air aging.[43] Oxidation Index values above 1.0-1.5 have been correlated to the loss of mechanical strength, which may lead to fatigue damage *in vivo*.[47, 68]

Representative photographs of cross sections of wear tested and accelerated aged acetabular components are shown in Figure 11. The aged, remelted HXPE components (Figure 11A) exhibited significant discoloration over the entire articulating surface and have lubricant penetration depth of about 1.5 mm. *Vivacit-E* HXPE components (Figure 11B) evaluated under the same conditions exhibited a slight discoloration at the pole and the fluid penetration depth was not measurable. These tests demonstrate that *Vivacit-E* HXPE is resistant to oxidation caused by lipid absorption.[43]

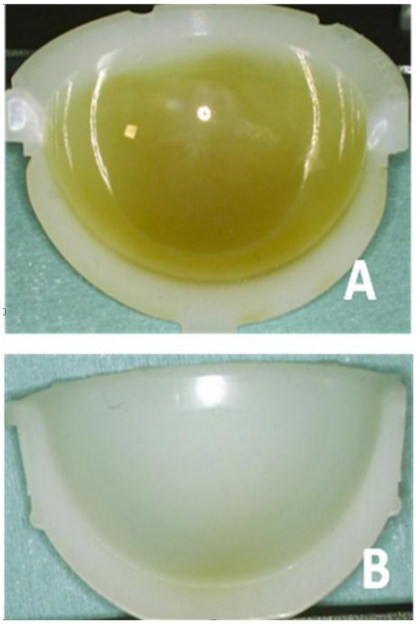


Figure 11. 45 million cycle (Mc) wear tested and accelerated aged liners of remelted HXPE (A) and *Vivacit-E* HXPE (B) showing the extent of fluid penetration.[56]

Ultra–Low Wear

For hip applications, *Vivacit-E* HXPE's predecessor, *Longevity* HXPE, has demonstrated ultra-low wear performance both clinically and through in vitro simulator testing.[11,13,57] To obtain similar crosslink density and wear performance, *Vivacit-E* HXPE has a comparable effective e-beam irradiation dose to *Longevity* HXPE. *Vivacit-E* HXPE was found to exhibit a 96% reduction in wear compared to gamma-irradiated conventional polyethylene (Figure 12) and comparable wear to clinically proven *Longevity* HXPE after the standard required 5 Mc in vitro testing.[2,9-11] In order to prove *Vivacit-E* HXPE's long-term ultra-low wear properties, the same test was extended to 75 Mc (Figure 13). *Vivacit-E* HXPE exhibited stable and low wear results even after long-term in vitro simulator testing.[44]

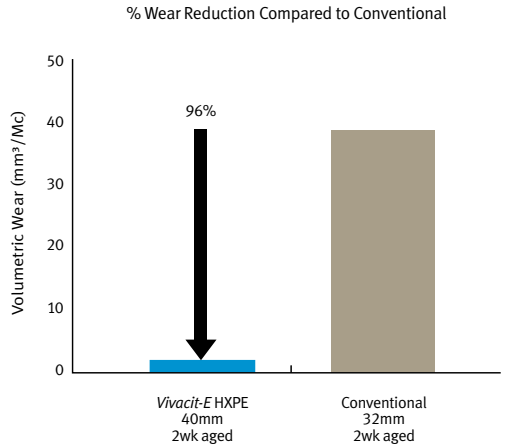


Figure 12. 12 station AMTI hip simulator in accordance with ISO 14242-1.[9-11]

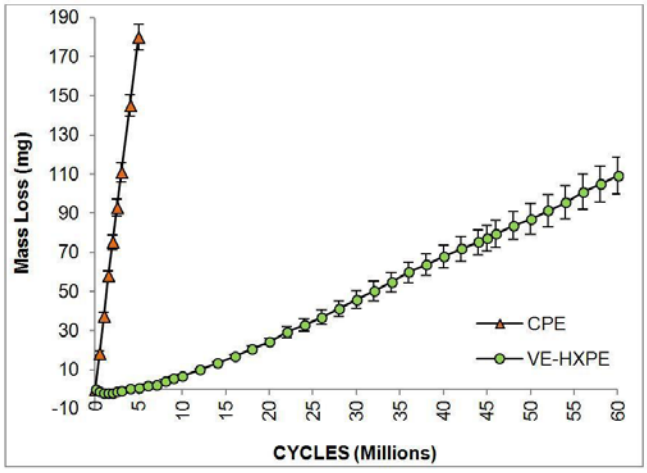


Figure 13. 12 station AMTI hip simulator in accordance with ISO 14242-1. [44]

With respect to knee applications, *Vivacit-E* HXPE was evaluated in both partial (UNI) and total (TKA) knee applications. After accelerated aging and 5.0 Mc of standard in vitro wear testing, the *Vivacit-E* HXPE exhibited a 90% and 96% reduction in wear in the UNI and TKA applications respectively compared to gamma irradiated conventional polyethylene in the same design (Figure 14).[58] Compared to Zimmer's previous highly crosslinked polyethylene for knees (*Prolong* HXPE), *Vivacit-E* HXPE further exhibited a reduction in wear of 73% (Figure 14).[58] In addition, the average equivalent circular diameter (ECD) of the particles generated throughout the in vitro wear testing across all designs and materials were comparable (Figure 15).[58]

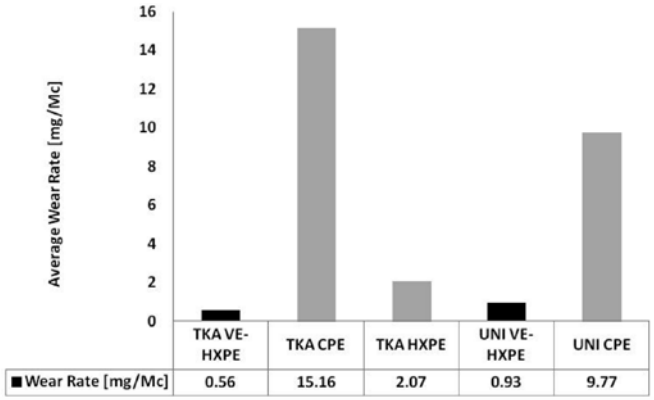


Figure 14. Comparison of Wear Rates [mg/Mc][58]

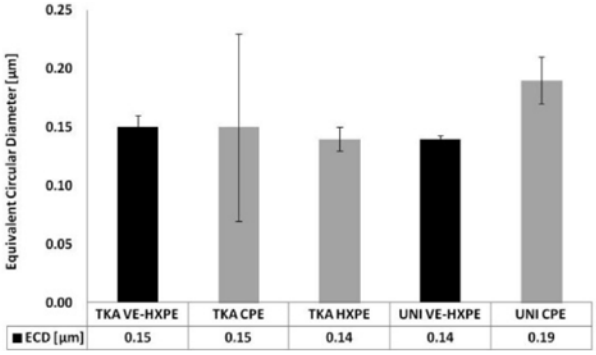
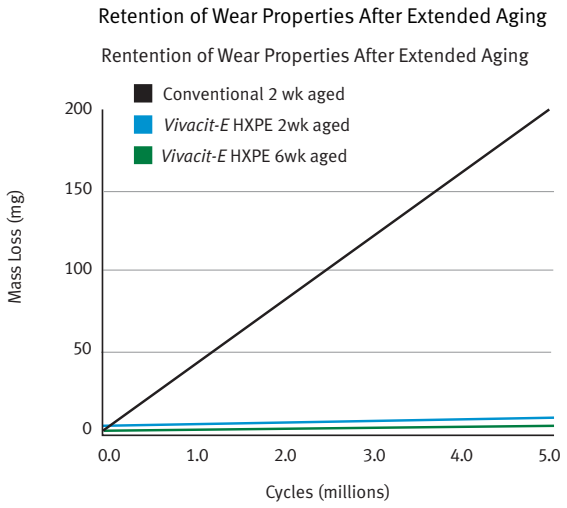


Figure 15. Comparison of Equivalent Circular Diameter (ECD) in wear debris salvaged at 1.0 Mc [µm].[58]

Wear Properties Maintained After Extensive Accelerated Aging

Oxidation of polyethylene has been found to lead to increased wear.[5-7] In order to prove that the wear properties of *Vivacit-E* HXPE are maintained and the material is resistant to oxidative aging, *Vivacit-E* HXPE acetabular liners were accelerated aged for 2 and 6 weeks (ASTM F2003) followed by 5.0 Mc of in vitro wear testing per ISO 14242. The volumetric wear rates for 2- and 6-week aged *Vivacit-E* HXPE were found to be statistically equivalent and demonstrated a 96% improvement over 2-week aged gamma-irradiated conventional polyethylene (Figure 16).[9]



12-station AMTI hip simulator in accordance with ISO 14242-1 at a frequency of 1.0±0.1 Hz.

Figure 16. Wear simulator testing showing no statistical difference between 2 week aged and 6 week aged *Vivacit-E* hip liners. 12 station AMTI hip simulator in accordance with ISO 14242-1.[9]

Improved Strength

The remelting process in *Longevity*® and *Prolong* HXPEs is designed to provide oxidative stability, but results in a slight reduction of mechanical strength. Since *Vivacit-E* HXPE is stabilized with Vitamin E and not remelted, it maintains the strength of gamma-irradiated conventional polyethylene, as shown in Figures 17 and 18. Due to *Vivacit-E* HXPE's continuous prevention of oxidative aging, the strength of the material is maintained even after extreme accelerated aging.[8,12,13]

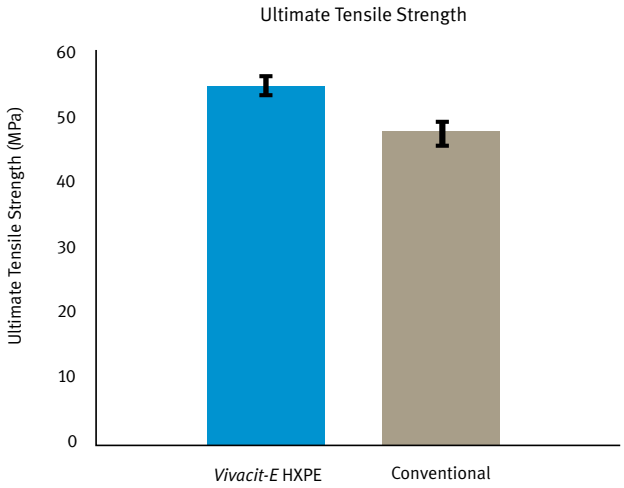


Figure 17. Comparison of Ultimate Tensile Strength.[12, 13]

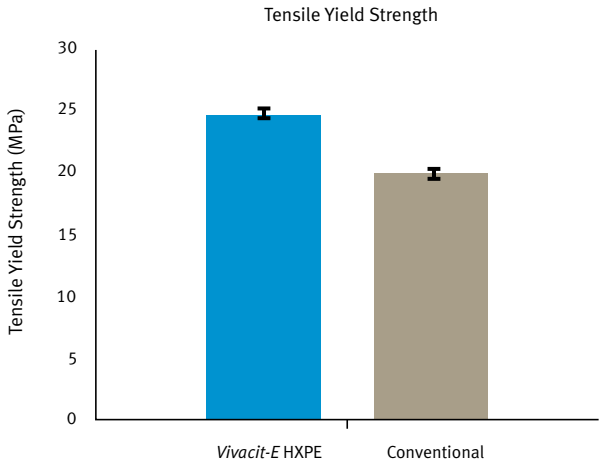


Figure 18. Comparison of Tensile Yield Strength.[12,13]

Hip Applications

Vivacit-E HXPE acetabular lines were also subjected to clinically relevant forces. Neutral and elevated-rim *Vivacit-E* HXPE acetabular liners were fatigue-loaded at orientations representing cup placement angles of 20°, 40° and 60° of inclination with 20° of anteversion. All liners completed fatigue testing without evidence of fracture (Figure 19).[45]

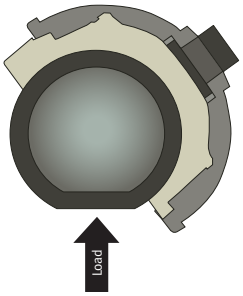


Figure 19. Anatomic fatigue testing at inclinations of 20°, 40° and 60° and 20° of anteversion.[45]

Knee Applications

Vivacit-E HXPE articular surfaces were subjected to forces that simulate activities of daily living. Posterior stabilized (PS) articular surfaces were evaluated to determine the durability of the spine in resisting shear fatigue failure under adverse loading conditions. The test set-up (Figure 20) simulated adverse hyperextension of the femoral component (7° flexion of the femoral component, 3o posterior tibial slope of the tibial baseplate). A comparison of the fatigue strength was then determined between an articular surface manufactured from *Vivacit-E* HXPE and one from a different design manufactured from gamma-sterilized CPE. There was a 9.6% increase in fatigue strength with the *Vivacit-E* HXPE component compared to the gamma-sterilized CPE component.[60]

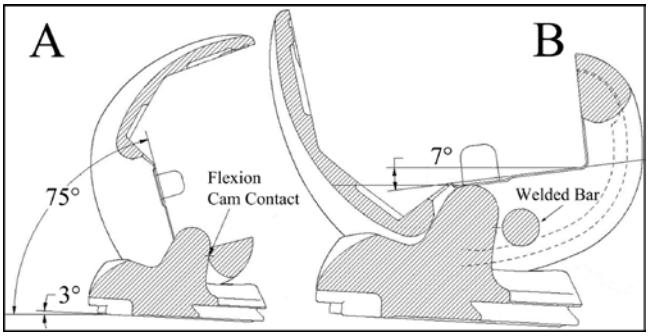


Figure 20. Specimen layouts describing posterior cam/spine contact at 75° flexion (a), welded bar to mimic contact (b), and component orientation.[60]

Biocompatibility

While HXPE and Vitamin E have been proven to be biocompatible with the human body, it is important to demonstrate the biocompatibility of any new implantable material. In order to prove *Vivacit-E* HXPE's biocompatibility, extensive testing was performed according to International Organization for Standardization (ISO) 10993 standards (Figure 21). *Vivacit-E* HXPE passed all tests, showing benign inflammatory response and no local toxicity effects.[28-38]

ISO 10993 Biocompatibility Tests	
ISO Standard/Test Description	**Results**
10993-5 Cytotoxicity	No evidence of causing cell lysis or toxicity
10993-11 Acute Systemic Toxicity	No evidence of systemic toxicity
10993-10 Max Sensitivity	No evidence of causing delayed dermal contact sensitization
10993-10 Intracutaneous	Met all requirements of the test
10993-3 Genotoxicity	Did not induce micronuclei
10993-11 (13) Week Systemic Toxicity	No evidence of systemic toxicity
10993-6 (2) and (12) Week Muscle Implantation	Classified as a non-irritant
10993-11 (26) Week Systemic Toxicity	Classified as a non-irritant

Figure 21. Biocompatibility tests performed according to ISO 10993 standards.

Biological Response to Wear Debris

In addition to the ISO 10993, the biological response to wear debris generated by *Vivacit-E* HXPE was evaluated in an animal study. Billions of wear particles were injected into each rabbit knee joint and the animals were sacrificed after 3 and 6 months. The biological response to the wear particles was assessed locally and systemically by clinical observations, body weights, hematology, macroscopic observations at necropsy and histological evaluations of tissues and organs such as kidneys and lymph nodes. *Vivacit-E* HXPE particles did not elicit adverse biological reactions and *Vivacit-E* HXPE was classified as a non-irritant.[28,29]

Comparison of Vivacit-E HXPE to Competitive Highly Crosslinked Polyethylene Processes

Incorporation of Vitamin E: Blending vs. Soaking

There are two common methods used to incorporate Vitamin E into polyethylene. The first method is called "soaked" or "infused." Generally, in this process, crosslinked polyethylene blocks are soaked in Vitamin E at an elevated temperature for several hours (approximately 120°C). The Vitamin E-coated blocks are then placed into an inert oven and homogenized (baked) at 120°C until the Vitamin E diffuses through the thickness of the block. The physical infusion of Vitamin E results in a non-uniform distribution within the polyethylene matrix, which can cause non-homogeneous material properties. A Fourier Transform Infrared Spectrometer (FTIR) was used to identify and study the chemical composition of Biomet E1 soaked Vitamin E polyethylene inserts. This analysis showed a highly non-uniform distribution of Vitamin E across the insert thickness, demonstrating the difficulty of achieving Vitamin E uniformity with the soaking method (Figure 22).[26]

The second method, "blending," involves mixing Vitamin E into polyethylene powder prior to compression molding, producing a very uniform distribution of Vitamin E throughout the polyethylene. The blending process also allows for the Vitamin E concentration to be tightly controlled; this is important because a sub-optimal Vitamin E concentration can negatively affect material properties as well as the duration of oxidative stability.[50] The blending method is used in the manufacturing process of *Vivacit-E* HXPE. FTIR analysis shows that a tightly controlled, homogenous concentration of Vitamin E is achieved across the Zimmer *Vivacit-E* HXPE material (Figure 22).[27]

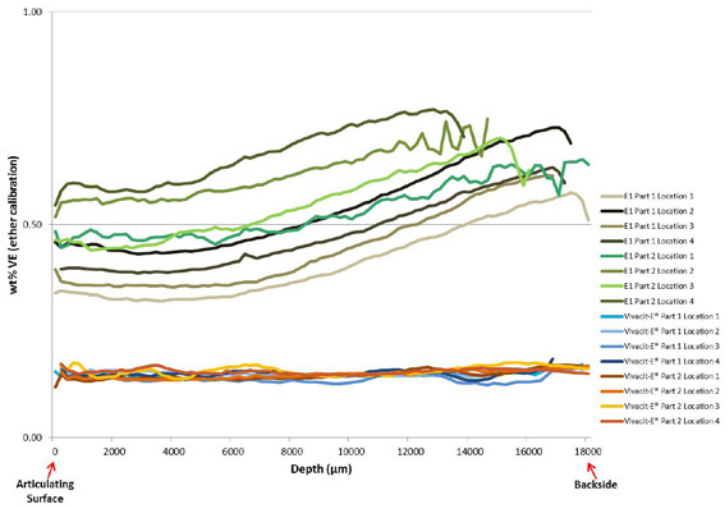


Figure 22. Non-uniform distribution of Vitamin E across Biomet E1 knee inserts compared to the uniform distribution of Vitamin E in *Vivacit-E* HXPE inserts.[27]

Another difference between the two methods is that the soaking method does not result in grafting during irradiation crosslinking. This is because the soaking process occurs after irradiation. In the blending method, irradiation occurs after the Vitamin E is incorporated into the material, allowing the Vitamin E to graft to the polyethylene. Vitamin E that is not grafted to the polyethylene has the potential to elute out of the material under load and motion.[27]

Irradiation Process: Gamma Irradiation vs. Zimmer's Warm E-Beam Irradiation Process

All non-Zimmer HXPEs use gamma irradiation for crosslinking. As a lower-energy irradiation source, gamm requires hours to achieve the target dose for HXPEs.[25] Since it is not possible to keep the polyethylene at an elevated temperature throughout the process, gamma irradiation does not permit warm irradiation.[25]

In contrast, e-beam delivers a high-energy stream of electrons to achieve the target dose in seconds, allowing the polyethylene to be irradiated at an elevatec temperature. Only Zimmer's proprietary e-beam irradiation process allows for warm irradiation. As previously mentioned, Vitamin E grafting is achieved through high dose, warm e-beam irradiation. Research by Massachusetts General Hospital, shown in Figure 23, demonstrates a significant increase in the percentage of grafted Vitamin E through warm versus cold irradiation.[1]

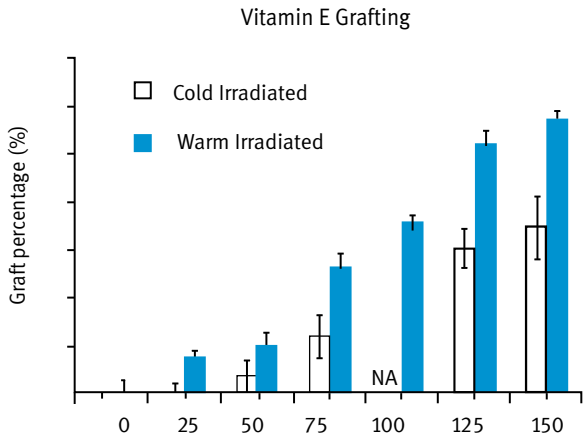


Figure 23. Increased Vitamin E grafting of warm irradiated Vitamin E HXPE over cold irradiated Vitamin E HXPE.[14]

Antioxidant Stabilized Polyethylene vs. Annealed Polyethylene - Retrieval Analysis of Stryker X3

Figure 24 shows the oxidation of a 7.1 year old Stryker X3 retrieval, with a maximum oxidation index above 1.5 on the articulating surface and over 7 on the backside.[4] Oxidation index values greater than 1.0-1.5 have been correlated to the loss of mechanical properties, which may lead to fatigue damage and possible subsequent failure *in vivo*.[47, 68]

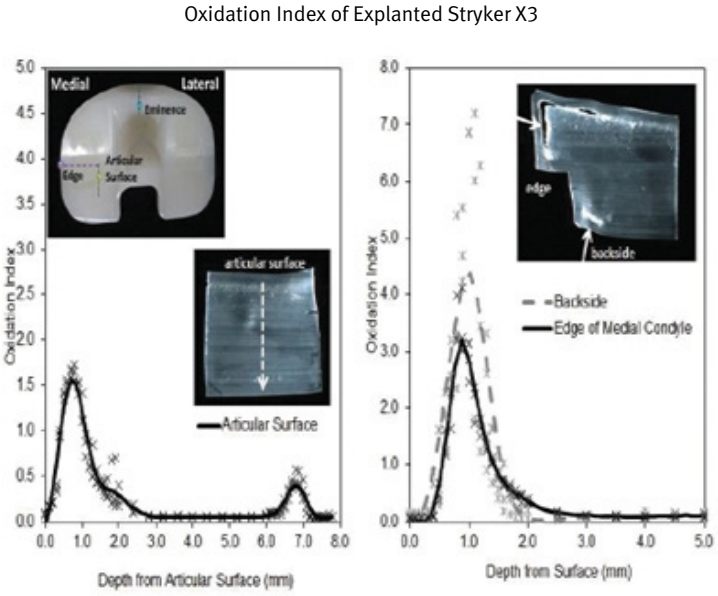


Figure 24. Oxidation of 7.1 old year Stryker X3 implant.[4]

The oxidation in the Stryker X3 implant was likely produced by residual free radicals remaining in the material and through the *in vivo* oxidation of absorbed lipids or free radicals generated during cyclic loading.

Aged and Unaged Small Punch Results Demonstrating *Vivacit-E* HXPE Strength Advantage Over Stryker X3 Liners

Small punch testing has emerged as a method of characterizing polyethylene mechanical properties and has the advantage of allowing testing on finished components due to the small size of test specimens. Small punch testing measures mechanical properties by looking at the deformation of small discs under loading conditions. Results are characterized by a load-displacement curve that provides total energy to failure (total area under the load-displacement curve), peak load, ultimate load and maximum displacement. Researchers have demonstrated a dependence on the area under the load-displacement curve to wear results of the material.[25]

Small punch testing was conducted on both unaged and aged Stryker X3 and *Vivacit-E* HXPE articular surfaces in order to compare the impact of aging on each material's mechanical properties. The Stryker X3 samples exhibited a 54% to 68% loss in mechanical properties when accelerated aged to 2 and 4 weeks, and had a total energy to failure after 4 weeks of aging that was 2.4 times less than 4-week aged *Vivacit-E* HXPE (Figure 25).[46]

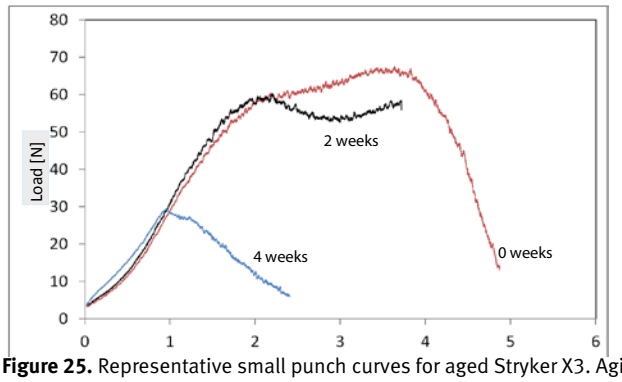


Figure 25. Representative small punch curves for aged Stryker X3. Aging weeks are shown on the Figure.[46]

The *Vivacit-E* HXPE samples exhibited no statistically significant change in properties over 33 weeks of accelerated aging (Figure 26), demonstrating the long-term strength advantage of *Vivacit-E* HXPE over Stryker X3 after accelerated aging.[46]

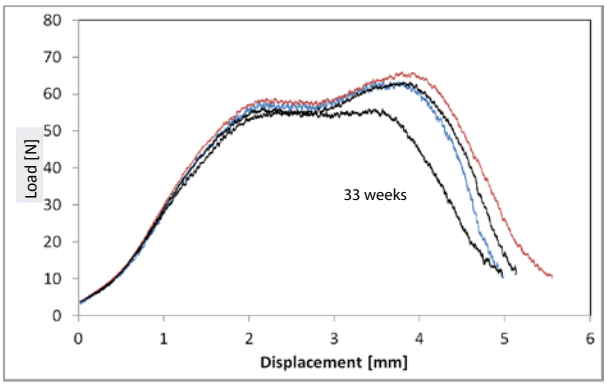


Figure 26. Representative small punch curves for *Vivacit-E* HXPE. Specimens aged from 0-33 weeks. There is no statistically significant difference between the aged and unaged samples.[46]

Head-To-Head Wear Testing Results Demonstrating Vivacit-E Wear and Oxidative Stability Advantage over Stryker X3

A further comparison of *Vivacit-E* HXPE and Stryker X3 was made through 5.0 Mc of in vitro wear testing of cruciate retaining TKA designs. Additionally, oxidation index (OI) values were determined prior to accelerated aging, after accelerated aging and after 5.0 Mc of in vitro wear testing. The in vitro wear test demonstrated that *Vivacit-E* HXPE exhibited a 39.6% reduction in wear compared to Stryker X3.[65] It was also determined that the Stryker X3 exhibited a significant increase in oxidation after 2 weeks of accelerated aging and another increase in oxidation after 5.0 Mc of wear testing. White oxidized polyethylene was observed on the base of the Stryker X3 component when sectioning for OI measurements following wear testing (Figure 27).[65] After wear testing and additional 2 weeks aging, the *Vivacit-E* HXPE still exhibited no oxidation whereas the Stryker X3 had average OI measurements between 0.77-1.12.[65]

Figure 27. Cross section films of HXPE-SA and VE-HXPE unaged, accelerated aged and 5.0 Mc of wear testing.[65]

Conclusion

The increased utilization of total hip and total knee arthroplasty in a younger patient population requires the orthopaedic industry to develop implants designed for long-term performance. To meet this need, *Vivacit-E* HXPE was developed to be Zimmer's longest-lasting and most durable polyethylene material, delivering on the three critical performance criteria of polyethylene without compromise.

Oxidative Stability

Vivacit-E HXPE actively and continuously prevents oxidation by incorporating an optimal quantity of Vitamin E, which is grafted directly to the polyethylene. The result is a polyethylene material with ultra-low wear and mechanical strength retention even after significant oxidative aging conditions.[8]

Ultra-Low Wear

High-dose e-beam irradiation results in *Vivacit-E* HXPE demonstrating a 94% wear reduction vs. gamma-irradiated conventional polyethylene and comparable ultra-low wear to clinically proven *Longevity* HXPE after an unprecedented 75 Mc of in-vitro hip simulator wear testing.[9-11] The *Vivacit-E* HXPE material also exhibited a 90% and 96% reduction in wear in the UNI and TKA applications respectively.

Improved Mechanical Strength

Vivacit-E HXPE does not need to be remelted after crosslinking because the Vitamin E present in the material prevents oxidation. This results in *Vivacit-E* HXPE having superior mechanical strength compared to *Longevity* HXPE and improved tensile strength compared to gamma-irradiated conventional polyethylene.[12,13]

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NOTE: E1 is a trademark of Biomet. X3 is a trademark of Howmedica Osteonics (Stryker)

NOTE: Bench testing is not necessarily indicative of clinical performance.