

**Lubrizol**

# Pathway™ Excipients

Thermoplastic Polyurethane (TPU) for Controlled Drug Release  
in Drug Eluting Devices and Implantable Drug Delivery



Lubrizol LifeSciences

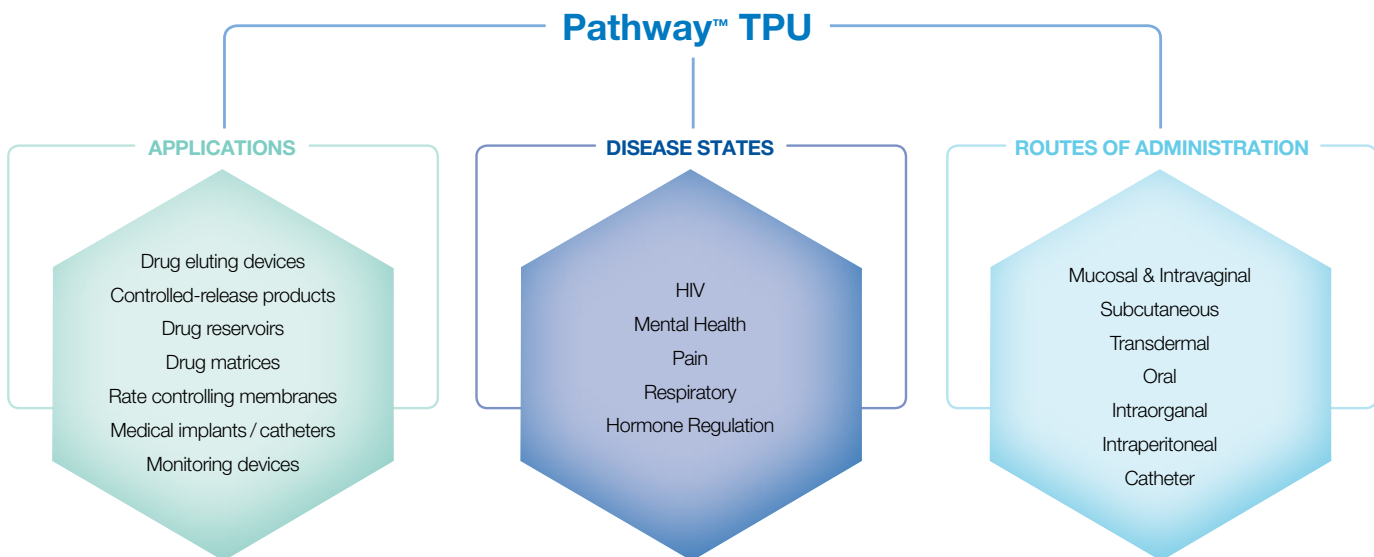
**Links Science to Life™**



## Pathway™ TPU Excipients

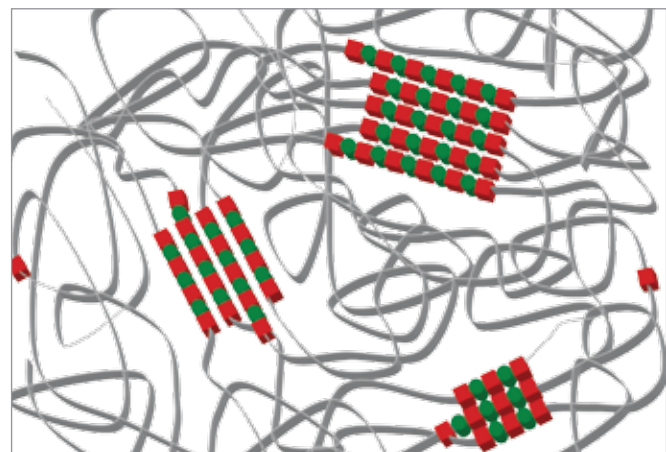
Whether you are interested in life cycle management or the development of new chemical entities, finding the right partner with the right polymer solution is an important first step. Lubrizol is the world's largest manufacturer of thermoplastic polyurethane products. Lubrizol's LifeSciences division provides the market with a wide variety of TPUs for use in medical device, pharmaceutical and combination products.

As pharmaceutical and device companies explore innovative solutions in a competitive market, combination products which go beyond the traditional industry boundaries are increasingly being utilized to provide product differentiation. Pathway™ excipients are pharmaceutical grade TPUs that provide drug and combination product developers with an innovative, versatile and customizable solution in disease states including HIV<sup>1-5</sup>, mental health<sup>6</sup>, pain (opioid)<sup>7</sup>, respiratory<sup>8</sup> and hormone regulation<sup>4</sup>.



## TPU Polymer Chemistry

Polymer chemistry is what makes TPU so adaptable. TPU is formed by step-growth polymerization between di-isocyanates and diols. In TPU, two types of diols contribute to the properties: a low molecular weight (low Mw) diol and a higher molecular weight (high Mw) diol. The polymeric diol and isocyanate groups aggregate to form discrete domains, referred to respectively as “soft segments” and “hard segments”. Soft segments contribute to the elasticity / flexibility of the TPU. The organization of hard segments form crystalline domains and physical crosslinks due to hydrogen bonding lending TPU its mechanical strength.



■ Di-isocyanate   ■ Low Mw diol   ~ Soft Block/Segment Polyol (high Mw diol)

## TPU Versatility

TPU has superior versatility when compared to other biocompatible, non-biodegradable polymers such as silicone or ethyl vinyl acetate (EVA). This versatility is imparted by the selection of the chemistry and the resulting properties of the soft and hard segments. When selecting the polymer chemistry it is important to consider the molecular weight and/or molecular volume of the active pharmaceutical ingredient (API) as larger molecules will progress more slowly than smaller molecules.

### Polymer Design Variables

- The polarity of the TPU soft segment may be changed by the choice of the high Mw diol
- The steric hindrance of TPU – that is, the forced path that an API must take through the polymer based on the polymer's spatial structure – may be changed by controlling a number of attributes including:
  - The quantity of hard segments
  - The distribution of the hard segments

Understanding how these design variables interact with an API becomes an essential aspect of drug delivery system development and is why partnering with a polymer chemistry expert like Lubrizol LifeSciences is advantageous.



Photo is courtesy of The Kiser Lab. Intravaginal ring employing both hydrophobic and hydrophilic TPUs for the sustained co-delivery of the microbicide tenofovir and contraceptive levonorgestrel.

## TPU Processing / API Incorporation

Drug loading can be accomplished by:

- Blending and then melt-processing the polymer and API by injection molding or extruding (this method typically applies to thermally stable APIs)
- Solvent casting (dissolving) or swelling the polymer and API in compatible solvents
- Filling preformed polymeric systems with API



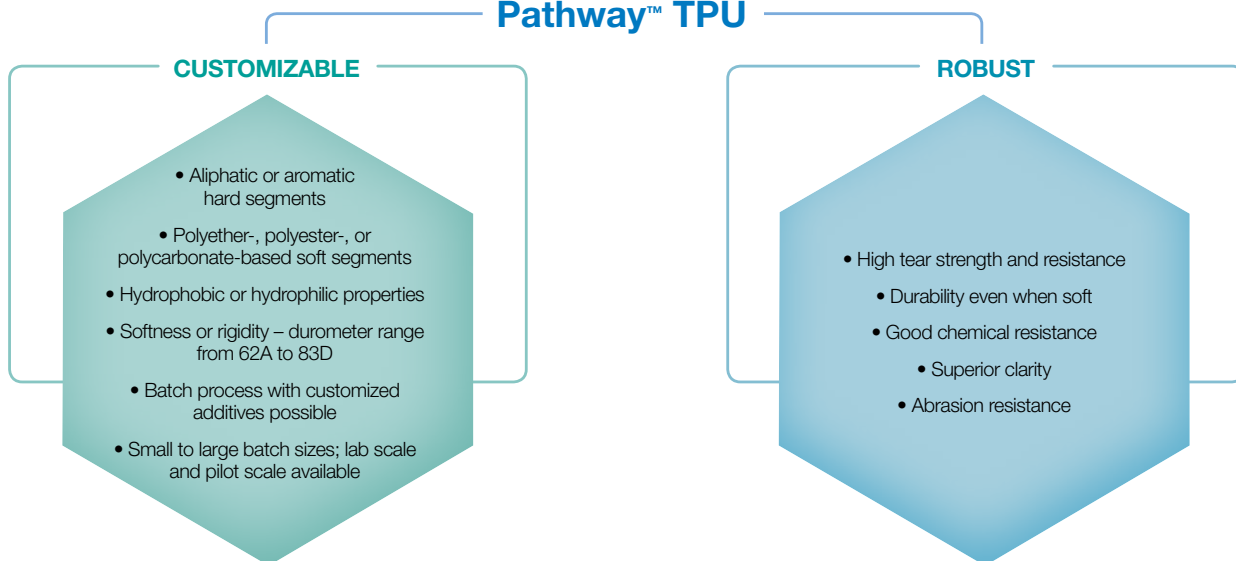
Axxia Pharmaceuticals' subcutaneous drug delivery system was developed to deliver and opiate continuously for 30 – 90 days with zero-order kinetics. Photo courtesy of Axxia Pharmaceuticals, LLC.

Upon cooling or after the evaporation of the solvent, the hard segments align, acting as pseudo cross-links, giving reinforcement and creating steric hindrance for the API during diffusion. Depending upon the properties of the API and the polymer, the API may associate mostly with the soft segments or with both the soft and hard segments.

The following sterilization methods can be used with TPU:

- Ethylene oxide
- Hydrogen peroxide
- E-beam radiation
- Gamma radiation

## Pathway™ TPU



## Pathway Product Portfolio

The variety of Lubrizol's TPU portfolio is unsurpassed – and with more than 30 years in the medical field and over 35 years in pharmaceutical arena, our experience is unmatched. As a technology-driven company, we have the expertise to tailor the polymer to meet your drug delivery requirements. By altering the crystallinity, the polarity or both we can provide TPUs that when combined with an API can deliver zero-order, Fickian-diffusion-driven or hybrid-release profiles.



Our TPU portfolio includes both aliphatic and aromatic varieties with polyether, polyester, and polycarbonate types. The most popular pharmaceutical grade polymers requested for drug delivery are:

- **Pathway™ hydrophobic polymers** – Aliphatic polyether TPU available in a variety of durometer, color and radio opaque grades
- **Pathway hydrophilic polymers** – Aliphatic polyether TPU formulated to absorb water from 20% to 1,000% by weight of the dry resin, while maintaining many of its mechanical properties

## Safety & Biocompatibility

Polyurethanes have been demonstrated to be biocompatible and stable in vivo and, as a result, have been used in biomedical devices for decades. Examples include implanted cardiac pacemakers and defibrillators, vascular prostheses, tissue adhesives and dermal wound dressings. Insulators for cardiac pacing leads and pacemaker headers are examples of longer-term implants that are designed to last many years.

The biocompatibility of Pathway aliphatic TPU materials has been evaluated extensively to insure that they pass the standardized tests for biocompatibility. The results in the table below show the types of tests and representative results that support the biocompatibility of these materials. TPU was included in a reference published for polyurethane for use in a vaginal sponge application on the U.S. Food and Drug Administration (FDA) Inactive Ingredient Database (IID). Pathway polymer excipients are safe and reliable for use in drug delivery systems. Extensive stability studies performed on select grades of Pathway polymers have found no significant change of physical properties or compositional profile.

## Representative Biological Test Results

Biological Test		Results
ISO 10993-3	Ames Mutagenicity Assay	Non-Mutagenic
ASTM F 756-13/ISO 10993-4	Hemolysis (Direct and Indirect)	Non-hemolytic
ISO 10993-5	Cytotoxicity (MEM Elution)	Non-cytotoxic
ISO 10993-6	Irritancy (Intracutaneous Injections)	No significant biological reaction compared to control
ISO 10993-6	Implantation (Muscle)	No remarkable difference compared to control
ISO 10993-10	Kligman Maximization Test (Skin Sensitization)	0% sensitization (Grade 1)
ISO 10993-11	System Toxicity	Not different from control

## Quality & Regulatory Support

Pathway TPUs are manufactured in compliance with the IPEC-PQG good manufacturing practice guidelines for pharmaceutical excipients, which is critical in assuring the safety, quality and efficacy of medicines.

Consistent with the IPEC significant change guideline, Lubrizol maintains a thorough management of change protocol and customers are notified of any significant change that may impact the quality of the product. Lubrizol understands that assuring supply chain controls and traceability is important to our customers and cooperates with customers in providing access to quality system audits of Lubrizol facilities, including establishment of quality agreements according to mutually agreed upon terms. Lubrizol has established drug master files for select excipients to facilitate review of our customers' drug applications and has a process in place to expeditiously establish a Drug Master File for new excipients as needed.

## About Lubrizol LifeSciences

Lubrizol LifeSciences combines an in-depth understanding of functional polymer systems with a portfolio of specialty materials to deliver application-specific solutions. As a technology leader and an established provider of pharmaceutical polymers, Lubrizol is your custom drug delivery system development partner. Together, we help link science to life.

## Technical Collaboration

Lubrizol LifeSciences has the technical and formulation expertise as well as the global resources needed to achieve success. We work closely with every customer from the beginning to create complete, customized solutions. Superior R&D, analytical and product testing and technical experience enable us to deliver differentiated technologies that fulfill our customers' needs and create a competitive advantage.

## Formulation Expertise

Customers may take advantage of our polymer, formulation expertise and application labs for the development of drug delivery systems. We also offer field support services, responding to technical service questions and visiting customers to provide application support, technical seminars, testing assistance, processing advice and more.

## Compliant & Secure

Lubrizol LifeSciences is committed to ensuring patient safety, customer satisfaction and the quality of its products. Our regulatory team includes seasoned professionals who keep abreast of evolving regulatory trends globally, engage in industry partnerships and develop policy with regulatory agencies. With our proficient systems, regulatory knowledge and support services, we work with our customers and help with implementation of proactive regulatory strategies.



J3 Bioscience, Inc.'s (formerly ViroPan) lubricating intravaginal ring was developed to relieve the symptoms of vaginal dryness. It is a clear flexible ring made of Pathway™ Hydrophilic TPU and is intended to provide moisturizing relief for up to seven days without the use of drugs or hormones. Photo courtesy of J3 Bioscience, Inc.

## Proven Performance

Lubrizol has a long history of manufacturing and supplying excipients for use in varied pharmaceutical dosage forms. In addition to Pathway excipients, Lubrizol's Carbopol® polymers were introduced 50 years ago and have been in global commercial use in many industries – including the pharmaceutical industry. Established pharmaceutical uses of Carbopol excipients range from rheology modifiers for topical and liquid products to applications in oral solid dose products (tablets and capsules) as binders and modified-release agents. The FDA has approved products containing carbomer polymers for over 35 years.

Please visit our website at [www.lubrizol.com/lifesciences](http://www.lubrizol.com/lifesciences) for additional information and inspiration.

## Global Presence

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Our global presence links you to even more opportunities by supporting growth in emerging markets, maintaining global supply and understanding international regulatory requirements.



## Global Locations

- Headquarters
- Regional Office
- Manufacturing
- Technical Center

## About Lubrizol

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The Lubrizol Corporation works at the molecular level to design performance characteristics into unique formulations that our customers use to differentiate their products. We combine complex, specialty chemicals to optimize the quality, performance and value of their products while reducing their environmental impact. We are proud to serve a global customer base that comprises a wide range of multinational and regional market leaders, including oil marketers and leading manufacturers of industrial and consumer products. Our mission is simple: to be an essential ingredient in our customers' success through collaboration, applied science and demonstrated value.

## References

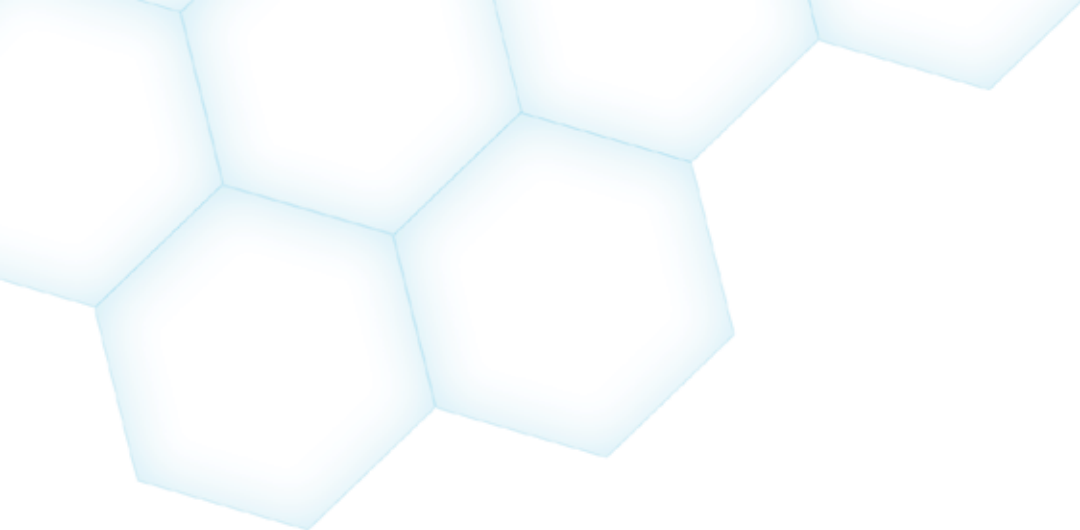
1. Clark MR, Johnson TJ, McCabe RT, et al. A hot-melt extruded intravaginal ring for the sustained delivery of the antiretroviral microbicide UC781. *J Pharm Sci.* 2012;101(2):576-587.
2. Johnson TJ, Clark MR, Albright TH, et al. A 90-day tenofovir reservoir intravaginal ring for mucosal HIV prophylaxis. *Antimicrob Agents Chemother.* 2012;56(12):6272-6283.
3. Johnson TJ, Gupta KM, Fabian J, Albright TH, Kiser PF. Segmented polyurethane intravaginal rings for the sustained combined delivery of antiretroviral agents, dapivirine and tenofovir. *Eur J Pharm Sci.* 2010;39(4):203-212.
4. Clark MR, Clark JT, Johnson TJ, et al. Development and pharmacokinetics of a 90-day intravaginal ring for the sustained co-delivery of the microbicide tenofovir and contraceptive levonorgestrel. Poster presented at: Annual Meeting of American Association of Pharmaceutical Scientists; November 10-14, 2013; San Antonio, Texas. Poster T2063.
5. Chen Y, Tratore YL, Li A, et al. Development of polyether urethane intravaginal rings for the sustained delivery of hydroxychloroquine. *Drug, Design, Development and Therapy* 2014;8:1801-1815.
6. Schwarz A, Thoroughman S, Winstead D, Decker S, Varughese J. Development of a subcutaneous implant using polyurethane as a semi-permeable membrane for the controlled release of risperidone. Poster presented at: Annual Meeting of the Controlled Release Society; July 15-18, 2012; Québec City, Canada. Poster 155.
7. Schwarz A, Thoroughman S, Winstead D. Polyurethane as a semi-permeable membrane for controlled release. Poster presented at: Annual Meeting of the Controlled Release Society; July 15-18, 2012; Québec City, Canada. Poster 194.
8. Subhaga CS, Ravi KG, Sunny MC, Jayakrishnan A. Evaluation of an aliphatic polyurethane as a microsphere matrix for sustained theophylline delivery. *J Microencapsul.* 1995;12(6):617-625.

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