



A One-Stop Shop for Intravaginal Rings

LLS Health partners with CONRAD to bring multipurpose IVR to the clinic

CONRAD is a biomedical research and development organization dedicated to improving the reproductive health of women, especially in developing countries. Founded in 1986 and based in Eastern Virginia Medical School (Virginia, USA), the non-profit develops and tests innovative, user-centered technologies to improve sexual and reproductive health globally. CONRAD's programs focus on prevention of HIV/STI, unintended pregnancies, and maternal and neonatal disease.

The product

Within CONRAD's pipeline is a first-in-class, multipurpose intravaginal ring (IVR) that combines levonorgestrel with tenofovir to provide contraception while preventing against acquisition of Human Immunodeficiency Virus (HIV) and Herpes Simplex Virus (HSV). Funded via US federal grants, the purpose of this novel device is to deliver multi-month contraceptive and HIV/HSV protection for women globally, and particularly those in resource-constrained countries who are unable to access healthcare easily or regularly.

"Many women in developing nations, and even in our country, are in remote communities, hours away from the nearest clinic, hospital, or pharmacy. As a result, it can be difficult for these women to access the medicines they need, resulting in missed doses or limited treatment options," explained **Dr. Meredith Clark, Senior Director of Operations**. "Our goal with this project is to serve the reproductive needs of women in general, and particularly those

in resource-constrained communities, delivering a single treatment option that offers months of protection against HIV, HSV, and unexpected pregnancy. Ultimately, we want to give women greater control over their reproductive health."

A fixed-dose combination product of this kind comes with challenges. The multipurpose ring combines two active pharmaceutical ingredients (APIs) in a single device, each with its own dosing requirements and compatibility issues.

To bring this novel concept into the clinic, CONRAD needed the support of a contract development and manufacturing organization (CDMO) with specialized expertise in long-acting implant and IVR development. CONRAD partnered with the team at Lubrizol Life Science Health (LLS Health), leveraging their years of experience developing and manufacturing IVRs to scale-up the multipurpose ring technology.

The challenge

When CONRAD first approached LLS Health, they had a segmented ring design that was capable of releasing of both APIs at their target release rates over the course of three months. However, this technology had been developed in an academic lab and only evaluated in pre-clinical studies and a first-in-human trial. CONRAD needed a CDMO with more expertise in IVR manufacturing that could better support their need for expanded clinical supply. Each API had very different physicochemical properties and very different target release rates. To accommodate this, the intravaginal ring had a novel, sophisticated design:

- **The Levonorgestrel segment** of the ring consisted of a core-sheath co-extrusion incorporating two Pathway™ Thermoplastic Polyurethane (TPU) excipients. One TPU was combined with the drug, and the other was co-extruded as a membrane around the core to control diffusion, enabling close to zero-order release of the hormone over time.
- **The Tenofovir segment** of the ring consisted of a hollow Pathway™ TPU tube filled with an aqueous paste of tenofovir.

This segmented ring design provided much-needed flexibility in controlling drug release of each active independently. By modifying both the TPU chemistries and the dimensions of each segment, CONRAD was able to achieve their challenging drug loading and release targets *in vitro* and *in vivo*.

To deliver a scalable version of the ring, CONRAD needed a CDMO with multiple competencies. The ideal partner needed to be capable of providing and scaling several polymer processing techniques, including co-extrusion, tubing extrusion, ring welding, and assembly. At the same time, it needed to offer an array of secondary services, including analytical method development and validation, highly potent API (HPAPI) handling, and efficient and effective *in vitro* release testing.



"Before we came to LLS Health, it was difficult to find all the necessary competencies to develop the multipurpose ring. We had a complex supply chain consisting of several CDMOs and sub-contractors, which was difficult to manage and created logistical issues. LLS Health served as a one-stop shop for us, greatly simplifying the technology transfer and manufacturing process for our intravaginal ring," added **Dr. Timothy McCormick, Principal Quality and Regulatory Specialist**. "Having previously worked with LLS Health on long-acting drug product development, we knew that its team had expertise and experience across a range of disciplines. The company was an ideal partner capable of supporting and delivering every aspect of this project."

LLS Health served as a one-stop shop for us, greatly simplifying the technology transfer and manufacturing process for our intravaginal ring.

The solution

The intravaginal ring was transferred from CONRAD's initial CDMO to LLS Health in 2015, and LLS Health began working on optimizing the manufacturing process to supply material for clinical evaluation.

Several LLS Health's in-house processing techniques were harnessed to manufacture the multipurpose IVR. The company's co-extrusion processes were used for the contraceptive segment of the ring, and tubing extrusion and filling were employed for the anti-viral segment. Finally, induction welding was used to combine the two segments into a final ring. Providing all these services together streamlined the supply chain, enhancing efficiency.

In addition, LLS Health provided support as a supplier of its proprietary Pathway™ TPU excipients for the project. Both Pathway™ Hydrophilic TPU and Pathway™ Hydrophobic TPU excipients were used in early prototypes of the device, providing the chemical and mechanical flexibility needed to achieve CONRAD's therapeutic goals. The initial work by CONRAD and its academic partner helped pioneer the use of TPU in drug-eluting devices, and today, there are several long-acting projects utilizing Pathway™ TPU around the world.

By working directly with LLS Health as a supplier of both excipients and CDMO services, CONRAD was able to benefit from a further simplified supply chain. It was also able to access unique polymer expertise at the formulation development stage that could only come from the excipient manufacturer.

“

Dr. McCormick commented:

LLS Health supported us in developing robust manufacturing processes to deliver each component and manufacture rings effectively and efficiently.

Moreover, the LLS Health team integrated quality control and assurance from the very beginning of our project. This was crucial in designing methods and procedures that were amenable to scale-up, helping us to avoid issues in clinical supply.

”

The results

Using the manufacturing processes it developed, LLS Health enabled CONRAD to enter clinical trials with placebo rings in less than a year and active rings quickly thereafter.

This support kept the CONRAD's data-gathering on track while the LLS team focused on producing the active, multipurpose rings for future trials. The team has since produced, characterized, and delivered multiple batches of rings for phase I clinical studies.

Dr. Clark commented: “The LLS Health team provided us with comprehensive support throughout the project. Its experts were proactive and creative in streamlining manufacturing of our product. As a result, we've completed five additional clinical trials, conducted in a combined five countries, with products manufactured by Lubrizol. I can honestly say that we wouldn't be where we're at today if it weren't for the close partnership and expertise from the team at LLS Health.”

“

We wouldn't be where we're at today if it weren't for the close partnership and expertise from the team at LLS Health.

”





Looking ahead

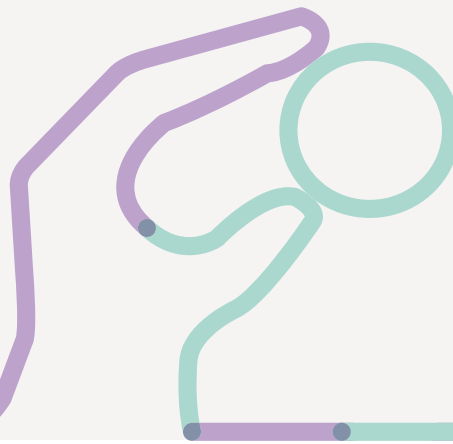
CONRAD's multipurpose intravaginal ring performed well in phase I clinical trials, and the organization is currently in discussions with the LLS Health team regarding next steps on this exciting project. Once funding is secured, both CONRAD and LLS Health are looking forward to working together again to scale up manufacturing for advanced clinical trials.

Dr. Clark concluded:

LLS Health has proved itself a capable and supportive partner in long-acting drug product manufacturing. We are excited to continue working with the team at Lubrizol to help us take our intravaginal ring closer to regulatory approval and reach the patient populations that need it most. With LLS Health's support, we look forward to delivering new methods of HIV prevention and contraception to women around the world.



Learn more about LLS Health's experience developing and manufacturing long-acting drug products at [our website](#).



Learn more about the multipurpose IVR and CONRAD's global mission of improving women's health at [conrad.org](#).



9911 Brecksville Road
Cleveland, OH 44141-3201 USA

[LubrizolCDMO.com](#)

The information contained herein is believed to be reliable, but no representations, guarantees or warranties of any kind are made as to its accuracy, suitability for particular applications or the results to be obtained. The information often is based on laboratory work with small-scale equipment and does not necessarily indicate end-product performance or reproducibility. Formulations presented may not have been tested for stability and should be used only as a suggested starting point. Because of the variations in methods, conditions and equipment used commercially in processing these materials, no warranties or guarantees are made as to the suitability of the products for the applications disclosed. Full-scale testing and end-product performance are the responsibility of the user. Lubrizol Advanced Materials, Inc., shall not be liable for and the customer assumes all risk and liability for any use or handling of any material beyond Lubrizol Advanced Materials, Inc.'s direct control. THE SELLER MAKES NO WARRANTIES, EXPRESS OR IMPLIED, INCLUDING, BUT NOT LIMITED TO, THE IMPLIED WARRANTIES OF MERCHANTABILITY AND FITNESS FOR A PARTICULAR PURPOSE. Nothing contained herein is to be considered as permission, recommendation nor as an inducement to practice any patented invention without permission of the patent owner. Lubrizol Advanced Materials, Inc., is a wholly owned subsidiary of The Lubrizol Corporation.