

# Drug Development<sup>®</sup> & Delivery

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## EXPEDITING FORMULATION DEVELOPMENT!

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# DRUG DEVELOPMENT

## CAPTISOL® Executive



**Matt Foehr**  
Executive VP & COO

**Ligand**

“Much of Captisol’s business comes from approved drugs and pending products. In many instances, we see the potential for pharmaceutical companies to accelerate the regulatory filing process as well as significantly cut down on development costs. Reformulation can truly bring meaningful innovation to established medicines.”

## LIGAND: PROVIDING SOLUTIONS TO THE SOLUBILITY, STABILITY & COMPATIBILITY ISSUES IN THE PHARMACEUTICAL INDUSTRY

**L**igand has evolved into a unique biopharmaceutical company with a model of creating a myriad of revenue streams that arise from many segments within the pharma universe. In January 2011, Ligand recognized the increasingly important role of the drug reformulation segment in the pharmaceuticals industry and completed its acquisition of CyDex Pharmaceuticals and Captisol®. The Captisol technology platform was originally created and patented by scientists from the University of Kansas and subsequently exclusively licensed to CyDex. Captisol’s powerful formulation potential has enabled five FDA approved products, including Pfizer’s VFEND® IV and Baxter International’s Nextertone®. There are currently more than 20 Captisol-enabled® products in development, including programs partnered with The Medicines Company, Merck, Bristol-Myers Squibb (BMS), and Lundbeck. Drug Development & Delivery recently interviewed Matt Foehr, Executive Vice President and Chief Operating Officer of Ligand, to discuss Ligand’s Captisol-enabled® technology and its significant role in the pharmaceutical marketplace of today and tomorrow.

**Q:** For any of our readers who may be unaware, can you please tell them about Captisol?

**A:** Captisol is our patented, chemically modified cyclodextrin. Cyclodextrins are enzymatically modified starches with a wide range of applications in food, chemical, cosmetic, and pharmaceutical industries. Captisol is used to improve solubility, stability,

and bioavailability of active pharmaceutical ingredients (APIs). It also has the potential to influence other properties of a product, such as reducing site reactions and eliminating the use of toxic excipients that are commonly included in a formulation to solubilize highly insoluble active agents. Captisol is versatile across multiple molecule families and sizes. It’s a very safe material, which was a designed feature and is a key benefit of the Captisol-enabled

technology. And that claim is supported by extensive data in our Type IV and V Drug Master Files (DMFs).

***Q: What role do you see Captisol playing in the pharmaceutical and healthcare industries?***

**A:** Line extensions and reformulation have become increasingly valuable solutions to the issues related to market erosion due to generic competition and continued clinical and regulatory uncertainty. Captisol can enable new dosage forms of existing drugs.

There is also a lot of evidence to suggest that poor solubility in drug development is one of the leading challenges for pharmaceutical companies. Between 70% and 90% of drug candidates in pipelines are believed to have low solubility.

Captisol enables solubilization and is so important because it is not only a drug delivery platform, but one that also has the potential to impact health outcomes, dosage, administration, and possibly the cost of care.

***Q: Do Captisol-enabled products face the same clinical and regulatory challenges?***

**A:** Much of Captisol's business comes from approved drugs and pending products. In many instances, we see the potential for pharmaceutical companies to accelerate the regulatory filing process as well as significantly cut down on development costs. Reformulation can truly bring meaningful innovation to established medicines. I have seen this first-hand in my career - how slight changes to dosage form or optimization of how an active ingredient is delivered in a clinical setting can bring major innovation to a product and have a positive impact on patients' lives.

A good example is Ligand's Propylene Glycol-Free Melphalan product, which we plan to progress into its Pivotal Clinical Trial next year. Propylene-Glycol-Free Melphalan was granted Orphan Drug status by the FDA as a conditioning treatment for use in autologous transplant for patients with multiple myeloma. Our Captisol-enabled formulation would be a new IV formulation for Melphalan, which is currently

formulated and sold as Alkeran® for Injection. Captisol-enabled Melphalan completely avoids the use of propylene glycol, which has been used as a co-solvent in other formulations and has been reported to cause renal and cardiac side-effects that limit the ability to deliver higher quantities of intended therapeutic compounds. The use of the Captisol technology to reformulate melphalan is anticipated to eventually allow for longer administration durations and slower infusion rates, potentially enabling clinicians to safely achieve a higher dose intensity of pre-transplant chemotherapy.

***Q: Why should the pharmaceutical industry be interested in Captisol?***

**A:** Captisol's success is primarily based on solving drug formulation problems, particularly in the area of parenteral delivery, oral, nasal, and inhalation formulations. Based on a number of high-profile partnerships - like Pfizer, BMS and Merck, we believe Captisol is a proven and powerful technology for our industry. Ligand acquired and is continually adding to our extensive DMFs to which our partners can refer to when

filing with regulatory agencies around the world. In addition, Captisol is covered by two Orange Book listable patents that offer some partners extended patent protection for their products. Ligand also has an exclusive and very productive partnership with Hovione FarmaCiencia SA to manufacture Captisol. We have a 50-metric ton capacity for Captisol now and the ability to significantly increase that capacity. Hovione's manufacturing operations allows us to have a steady stream of reliable cGMP supply.

***Q: Is there existing clinical data relating to Captisol's safety?***

**A:** Captisol has been tested in more than 100 clinical and safety studies reported in our Type V DMF. It appears safer than other cyclodextrins and is, we believe, of a higher quality than other cyclodextrins. Captisol was specifically designed to be safe and well tolerated. There are a number of studies that report, for example, that Captisol can control the physical stability of proteins, which is a growing concern in the pharmaceutical industry, especially with the growing number of protein-

based biopharmaceuticals currently in development.

***Q: How has Ligand's business model played in the marketing and licensing of Captisol?***

**A:** The Captisol technology was really a great fit for Ligand. The business model at Ligand is all about partnering to create a large portfolio of potential revenue streams. Ligand now has over 50 fully funded partner-driven programs in various stages of development, and Captisol is obviously a technology built to be partnered. We have relationships with a large number of companies, and introducing the Captisol technology into these conversations has been very fruitful. Ligand plans to take the Captisol brand to a new level and really exploit the aspect that this is a validated, patented, enabling technology.

***Q: What are some of the partnerships you have with Captisol-enabled products?***

**A:** We have partnerships with more than 25 companies that span in all phases of development. Our

collaboration with Onyx Pharmaceuticals began in 2005 to explore the use of Captisol technology as a method to create an IV formulation of Carfilzomib. Carfilzomib is a next-generation proteasome inhibitor for the potential treatment of patients with relapsed and refractory multiple myeloma. Multiple myeloma is the second most common hematologic cancer. In the US, more than 50,000 people are living with multiple myeloma, and approximately 20,000 new cases are diagnosed annually. Recently Onyx announced its plans for submission of an NDA for Carfilzomib.

A January 2006 article in this journal, titled Partnering with Big Pharma, reviewed our established long-time relationship with Pfizer in bringing forth this technology out of the University of Kansas, from which several products have been realized including VFEND® IV, Cerenia®, and Geodon® products. The active ingredient in VFEND, voriconazole, is known to be extremely insoluble. Captisol enabled an IV formulation to be developed for this product that treats invasive fungal infection. I believe VFEND IV would not be on the market if it weren't for Captisol. Cerenia is a veterinary health product

in which Captisol was able to increase the solubility to enable the product as well as provide an injection site tolerance, which was a major issue for Cerenia while it was in development. Geodon is a product used to treat symptoms for schizophrenia. It is also highly insoluble by itself. Captisol was able to increase the solubility of the active.

Baxter International recently launched Nexterone<sup>®</sup>, a product it acquired after its development through FDA approval by Prism Pharmaceuticals. Amiodarone, the active in Nexterone, is a commonly used anti-arrhythmic agent used for the treatment of ventricular tachyarrhythmias, or fast forms of irregular heartbeat. For Nexterone, we were able to design a formulation that eliminated the co-solvents and interest Prism in licensing and furthering the development of the product.

Lastly, Abilify<sup>®</sup> is a product marketed by Bristol-Myers Squibb in the manic bipolar arena. The solubility of the active was increased and at the same time, site reactions were reduced, solving major drug precipitation issues.

***Q: What are your criteria for securing the right partner, and what types of partnerships or deals are you working on now?***

***A:*** We are looking at forming broader platform relationships with partners who can truly leverage Captisol in many therapeutic areas. We see forming these sorts of platform relationships with companies that have libraries of compounds as being a really important way to grow the business in the long-term.

Following our acquisition of CyDex in January 2011, we now really have our arms around the Captisol business and have welcomed some valuable new colleagues from CyDex onto the Ligand team. Together we have already begun to realize that there is an enormous amount of potential partnerships waiting for Captisol. The name of the game here is to get programs moving into development so that product development teams at companies large and small can see how enabling the Captisol technology is, for advancing their programs toward the marketplace. Ligand deal structures really help make that possible.

***Q: Do you see other broader platform opportunities for Captisol?***

***A:*** We see a clear potential for forming broader platform relationships with pharmaceutical companies who can truly leverage Captisol. Captisol is a proven drug delivery system that has worked across several therapeutic categories involving small molecule and biotechnology drugs, including injectables, oral drugs, inhalations, nasal, and ophthalmic delivery. The possibilities are enormous.

Most of the drugs that get eliminated from a pipeline are often eliminated at the earliest stages when they are placed on the formulator's bench. Not only does Captisol have the ability to solve the solubility issues in many cases, but we have the ability to affect the entire formulation and therefore affect the outcomes that the products eventually see. ♦