

From Shelved Compound to Life-Saving Antibiotic

Cubist Pharmaceuticals, Inc. is a 400-plus employee biopharmaceutical company focused on the research, development and commercialization of products that address unmet medical needs in the acute care environment. Founded in 1992, Cubist celebrated 10 years as a NASDAQ listed public company in 2006 (ticker symbol: CBST).



To date, Cubist has been exclusively focused on developing business and product opportunities in the anti-infective marketplace. CUBICIN[®] (daptomycin for injection), the company's flagship drug, was approved on September 12, 2003, by the U.S. Food and Drug Administration (FDA), for sale in the United States. CUBICIN, a first-in-class (lipopeptide) IV antibiotic, was initially approved for the treatment of complicated skin and skin structure infections (cSSSI) caused by specific Gram-positive bacteria. Since its launch in November 2003, CUBICIN has tracked as the most successful launch of an IV antibiotic in U.S. history.

In May 2006, the FDA approved a supplemental new drug application for CUBICIN as a once-a-day therapy at 6 mg/kg for the treatment of *Staphylococcus aureus* (*S. aureus*) bloodstream infections (bacteremia), including right-sided endocarditis, caused by MSSA (methicillin-susceptible *S. aureus*) and MRSA (methicillin-resistant *S. aureus*). Cubist estimates that these infections account for 30,000 deaths in the U.S. alone each year. CUBICIN is the only IV antibiotic approved for this indication based on the results of a prospective, randomized, controlled registration trial. To date*, CUBICIN has been used in the treatment of an estimated 325,000 patients in the United States, alone.

The road from the laboratory bench to the hospital bedside, however, was not a smooth one. Daptomycin was discovered in the late 1970s by scientists at Eli Lilly and Company. Lilly had conducted Phase II clinical trials administering daptomycin at 2 milligrams per kilogram (mg/kg) every 24 hours and 3 mg/kg every 12 hours, but found the doses insufficient for certain more serious infections. In attempting to increase the dose to potentially improve efficacy, Lilly found that doses at 4 mg/kg every 12 hours caused skeletal muscle toxicity problems. In 1991, after 21 clinical trials, Lilly informed the U.S. Food and Drug Administration that it was voluntarily suspending human studies of daptomycin.

In January 1997, Cubist entered into discussions with Lilly after learning that Lilly had decided to cease development of daptomycin. Cubist scientists initially believed that the drug could be developed for topical application - either for application directly to the skin or by ingestion - to avoid the toxicity issues that were associated with systemic (IV)

* Through 6/30/07

administration. In November 1997, Cubist took a modest gamble[†] and licensed worldwide rights to daptomycin from Lilly.

Cubist scientists were on a mission. The late Francis (Frank) Tally, MD, who then served as Cubist's senior vice president and chief scientific officer, along with leaders in the infectious disease community, were very concerned about the lack of antibiotics in the pipeline of the large pharmaceutical companies. He knew that Gram-positive pathogens like *Staphylococcus aureus* were increasingly gaining the upper hand as resistance grew to "old reliable" antibiotics. He and others had shown the management of Cubist that the unmet need for new antibiotics, and "big pharma's" declining interest in antibiotic discovery and development had left a void that created a business opportunity. Cubist, however, needed to get a product candidate into the clinic quickly to prove to its shareholders (the company had recently gone public, with initial revenues based on research partnerships with big pharmaceutical companies) that they would see a return on their investment before too many years passed. Daptomycin had the potential to be a good drug if only they could succeed where Lilly had not.

Scientists at Cubist, led by Tally and Rick Oleson, DSc, were determined to understand what was causing the toxicity issue that Lilly had experienced in their trials. If it were possible to understand and solve the toxicity problem, daptomycin might still be useful as an IV antibiotic, which could have broader application than the topical formulation Cubist initially had contemplated. The conventional thinking was that the toxicity issues were caused by high concentrations of the drug in the blood. In 1998, Oleson and Tally designed studies that would elucidate the toxicity issues. Oleson and Tally demonstrated that, unexpectedly, the toxicity issues were related to dosing intervals. In particular, less frequent, e.g., once daily dosing minimized the adverse skeletal muscle effects Lilly had observed. Even better, this dosing schedule optimized efficacy, as additional research showed that CUBICIN's antibacterial activity was concentration dependent. That is, once daily dosing resulted in higher, and thus more effective, peak concentrations than divided doses throughout the day.

Based on this research, Cubist obtained FDA approval to resume human trials of CUBICIN as a once-a-day IV antibiotic. Cubist submitted a new drug application (NDA) for CUBICIN in December 2002, based on data from two Phase III clinical trials in complicated skin and skin structure infections. The FDA granted priority review and CUBICIN was approved in September of 2003. Following this approval, Cubist created its own commercial organization and launched CUBICIN in November of 2003.

The research that led Oleson and Tally to determine once-a-day dosing of CUBICIN broke through the deadlock that had stymied Lilly and unlocked a revenue stream for Cubist. In 1999, Cubist filed a "Method of Administration" patent application based upon the novel dosing regimen to minimize the adverse skeletal muscle effects. It was recognized as a breakthrough innovation when, in October of 2002, the United States Patent & Trademark Office granted the initial patent on their dosing discovery.

This innovative thinking and the company's perseverance has taken this small company of approximately 40 employees in 1997 to what it is today – a successful,

publicly traded company with a growing revenue stream from the success of CUBICIN. Today, CUBICIN is marketed in the United States by Cubist Pharmaceuticals and outside the United States by various marketing partners. This growing revenue stream is fueling the development of new anti-infective drug candidates, as the company is building its pipeline from internal discovery, as well as external sources.

† *Attractive terms were negotiated—a low up front payment and a royalty to Lilly if the product got to market.*

