CASE STUDY

Partnering With Big-Pharma: Pfizer & CyDex's Positive Experience: A Case Study

By: Contributor Guy Furness

BACKGROUND

For many technology companies, it is a source of eternal frustration that pharmaceutical partners insist on anonymity when they enter into R&D agreements. A pharma company even allowing broad details of the agreement's scope to be printed in the press release announcing it represents a rarely seen gesture to its collaborator.

Yet at the Ninth Annual Drug Delivery Partnerships Conference in San Diego, California, earlier this year, Pfizer's Associate Research Fellow in PRD, Dr. John Crison, took his place on the podium alongside Dr. Diane Thompson, Co-Founder and Chief Scientific Officer of CyDex Inc, to give a joint presentation about the application in life-cycle management strategies of CyDex's drug solubilizing technology.

That corporate-giant Pfizer deigned to co-present with its partner spoke volumes about the long-standing relationship between the two companies. After almost a decade-and-a-half, many real-life lessons have been learned by both parties about how to maintain such a close relationship successfully. Importantly, CyDex has learned how best to fit its crucial partnership with Pfizer with the development of its business independently of this valued partner. Achieving this balance is important for any technology company involved in a major agreement with a large pharma partner, but it is not easy.

Pfizer's relationship with CyDex began back in 1991 when Pfizer UK identified a clinical need for an intravenous infusion of the antifungal compound, voriconazole, which was also being made available as an oral tablet. Although the requirement for an intravenous line extension was clear, the low solubility of voriconazole meant that achieving a concentration high enough for an intravenous dosage form presented a significant technical challenge.

The R&D team knew that cyclodextrins worked well as solubilizing agents for their compound, but hydroxypropyl-β-cyclodextrin (HP-CD) was not available for licensing because a competitor, Janssen, owned it. They therefore needed to find a new solubilizing agent.

THE CAPTISOL® TECHNOLOGY IN BRIEF

CAPTISOL®, the chemical name of which is sulfobutylether 7-β-cyclodextrin (SBE7-β-CD), was invented at the University of Kansas Higuchi Bioscience Center for Drug Delivery in 1990. CyDex, based in Lenexa, Kansas, was founded in 1993 to establish the technology.

Captisol is a donut-shaped molecule with a hydrophilic exterior and a hydrophobic interior. A solid, insoluble drug molecule in an aqueous environment is generally regarded as lipophilic. In the presence of Captisol, such lipophilic molecules readily fit into the lipophilic center or the cyclodextrin molecule to form a 1:1 drug-cyclodextrin complex. The hydrophilic exterior of the complex means that the drug-cyclodextrin complex is water-soluble.

Currently, there are more than 20 open INDs (or equivalents outside the US) for the study of Captisol (two of these are CyDex compounds) and more than 400 pharmaceutical and biotechnology companies are using the technology in the development of their compounds, for delivery via various routes. At the same time, CyDex is progressing toward a specialty pharma model, with multiple Captisol-enabled drug products under development in-house.

PFIZER'S CRUCIAL DECISION

Pfizer quickly identified sulfobutylether 7-β-cyclodextrin (SBE7-β-CD) (CAPTISOL®), under development at the University of Kansas, as the key to enabling its intravenous antifungal to reach the market, where it had the potential for sales in excess of $100 million. However, Captisol was a novel technology in the early stages of development, and therefore carried inherent risk.

It was at this stage that Pfizer made a crucial decision. It weighed up the additional risks and pitfalls of a drug delivery deal and development partnering, which included bringing a new technology forward, against the fact that this technology fitted exactly with the current unmet need. The potential benefits won.

TThe resulting agreement between Pfizer and CyDex, the company which had been spun out of the university to develop the SBE7-β-CD technology, gave Pfizer exclusive rights to antifungals that used SBE7-β-CD and a non-exclusive license to develop other Pfizer compounds using the technology.

The process was to be transferred and scaled up at Pfizer, and the two partners would co-own the manufacturing process and all safety data their collaboration generated. CyDex retained full and independent rights to license its technology to industry.

Dr. Crison explained how, as the alliance grew, the emphasis began to shift from project management toward corporate-scale management. Among the various areas that the partnership's structure had to

TABLE 1

Pfizer & CyDex Both Carried Out Preclinical Captisol® Safety Studies

Pfizer Conducted:	CyDex Conducted:
General Pharmacology	Monkey & Rat Continuous IV Infusion Studies (4-day & 14-day continuous)
Pharmacokinetics & Disposition	Monkey & Mice SC Studies (90-day)
Genotoxicity	Rodent Oral Gavage Studies (1-day, 7-day, 28-day, 90-day)
Bolus IV Rodent Studies (14-day, 30-day, 180-day)	Dog Oral Gavage Studies (1-day, 7-day, 28-day, 90-day)
Bolus IV Dog Studies (14-day, 30-day, 180-day)	Rodent Inhalation Studies (1-day, 7-day, 28-day)
Bolus IV Reproductive Study in Rats & Rabbits (segments I, II & III)	Dog Inhalation Studies (1-day, 7-day, 28-day)

deal with were: IP and patents, legal, regulatory, financial, preclinical and clinical safety, Captisol manufacturing, new technology developments, and line extensions.

Dr. Crison also pointed out that both companies took a major role in most activities. For example, commercial-scale Captisol manufacturing was to be carried out by various companies. Pfizer established manufacturing both in-house and with Abbott; CyDex and Pfizer established manufacturing at 5-10 MT/year with PPG-Sipsy; and CyDex established manufacturing at >50 MT/yr with Hovione. The development of Captisol's preclinical safety package provides another example of how the two partners shared the workload (Table 1).

TANGIBLE RESULTS

In any successful collaboration, a good working relationship between the teams and personnel involved in an alliance is important, and a well thought-out and workable deal structure is of course vital. Another major requirement to ensure a long-lived, happy relationship is that it gets results.

To date, the alliance between Pfizer and CyDex has brought forward two major new Pfizer products, neither of which would have made it to market without the application of the Captisol drug delivery technology.

The first was the formulation of voriconazole that had originally prompted Pfizer to seek a solubilizing technology. It was successfully launched in 2002 as Vfend® IV, and comprises 200 mg of active compound in 16% Captisol at pH 6-7. Pfizer's financial results indicate Vfend (IV + oral) sold $287 million in 2004.

In 2002, Geodon IM (ziprasidone mesylate), the second Captisol-Enabled Pfizer product was launched for the treatment of acute agitation in schizophrenic patients. Dr. Crison said that the original target solubility for the IM formulation was around 40 mg/ml, but that the free base had a solubility in water of 0.0003 mg/ml. The use of a mesylate salt improved solubility in water significantly to 0.9 mg of free base/ml, but still did not bring it close to the target needed for it to represent a viable product. In contrast, using a 40% Captisol formulation, the mesylate salt had a solubility of 44 mg of free base/ml – well within the requirements. The final Geodon IM presentation comprised 20 mg of active compound in 30% Captisol.

MUTUAL BENEFITS IS KEY

Dr. Crison believes that the key to the success of Pfizer's relationship with CyDex is that it is mutually rewarding. Pfizer has gained multiple life-cycle management products, non-exclusive rights to the technology, access to CyDex oral and inhalation data, and CyDex manufacturers.

In exchange, CyDex sealed its first drug delivery systems deal, gained assistance with R&D from a major multinational pharma company, and has been able to use Pfizer's parenteral product data.

It is important to note that although Pfizer could have well afforded to acquire the Captisol technology outright, it only licensed the rights it required. This left the originators of the technology free to explore, research, and develop other applications, thus allowing the technology a chance to reach its full potential both within the realm of Pfizer's activities and beyond.

CASE STUDY

GROWING AN INDEPENDENT BUSINESS

While the agreement with Pfizer took a central role in the early growth of CyDex and remains central to the company today, it is essential that CyDex, like any company in a similar situation, maintains its independence through the growth of its business outside the partnership.

In fact, the Pfizer agreement plays an important part in making this possible. The first licensee of Captisol being Pfizer, a pharmaceutical giant, validates the technology somewhat, particularly because products have been launched. But in addition to the positive message sent out by having a major player as a partner, there are solid financial benefits. CyDex receives royalties on Pfizer's Captisol-Enabled products, with which it is able to fund the growth of its independent proprietary product development.

This strategy of reinvestment has enabled CyDex to initiate several proprietary product development projects across a range of delivery routes. One example is the application of Captisol in an oral solution. The conventional formulation was high in alcohol and had a bitter taste, and the label calls for it to be diluted in a drink before administration. Whereas the Captisol product was bioequivalent, alcohol free, presented ready to use with no need for dilution, and palatable. In another example of an oral application, Captisol allowed very insoluble compounds that precipitated at pH 6-7, to be formulated as osmotic and polymer-matrix extended-release tablets.

The third example – a nasal line extension of the sedative, midazolam (Versed®) performed at the University of Iceland – illustrated Captisol's application in a different healthcare setting. The nasal route was chosen because the product was targeted for use in the outpatient setting. The onset of action of oral Versed is 40 minutes, which was undesirable for outpatient procedures. Intravenous dosing is often not desirable.

For pulmonary delivery, Captisol has enabled corticosteroids to be formulated as solutions rather than suspensions. Solutions are easier to manufacture and sterilize, and are suitable for use with all types of nebulizers, including ultrasonic nebulizers.

SUMMARY

In summary, CyDex believes that the benefits of forming a close relationship with a major pharmaceutical partner are manifold. Indeed, it is more than simply a belief because they have proof in the form of a successful history, partnered with Pfizer, going back almost a decade-and-a-half. In addition, CyDex has license agreements with an additional 12 big pharma, biotech, and specialty pharma companies. CyDex also has Limited Clinical Use Agreements with 6 of the same group of companies.

Yet, having these relationships need not mean that the technology partner loses its independence. It is crucial for the success of the technology company that its major partner does not hamper growth. Far from inhibiting development, a major partnership should and can represent an enormous advantage. As CyDex and Pfizer have shown, if it is structured and managed well, such a relationship can be leveraged to help build the independent business.

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BIOGRAPHY

Mr. Guy Furness is an independent writer specializing in drug delivery. He has had articles on this subject published in various journals, industry magazines, and national newspapers, including four recent publications in The Times newspaper (UK), and has spoken on the subject of drug delivery at international conferences. He is founder of ONdrugDelivery Ltd, a niche industry information company that provides specialist writing and contract publishing services for its industry clients. The company also publishes information on the sector in detailed intelligence reports, and produces bespoke reports for individual clients with particular needs. Prior to ONdrugDelivery, Mr. Furness spent 1 year as a specialist freelance drug delivery writer and, before that, 2 years as Editor of Target World Drug Delivery News, which he helped conceive, set up, and launch in 2001. Mr. Furness began his career as a member of the editorial team of the pharmaceutical R&D products database, Pharmaprojects. He graduated from the University of Bath (UK) in 1998 with a BSc (Hons) in Natural Sciences.