EVOLVING INDUSTRY NEEDS REQUIRE EVOLVING PARTNERS: WELCOME THE SOLUTION PROVIDER VERSUS THE CMO

In this article, Steven Hamlen, Group Product Manager, Modified Release Technologies and Rao Tatapudy, PhD, Vice-President, Scientific Affairs, R&D, both of Catalent Pharma Solutions, and Thorsten Schmeller, PhD, Head of Global Marketing, New Products, Pharmaceutical Ingredients & Services in the Nutrition & Health Division of BASF (Ludwigshaven, Germany), discuss how companies that previously followed the traditional CMO model are increasingly moving toward becoming solution providers. They describe the drivers that have led to this innovation, as well as how solution providers have integrated technologies and innovative business partnerships into efficient solution offerings in place of historic sole contract manufacturing. A case study of this evolution to a total solution provider business model is discussed in relation to solubility enhancement, resulting in better treatments for patients and increased efficiency, as well as differentiated products for the pharmaceutical industry.

DRIVERS OF EVOLUTION TO SOLUTION PROVIDERS FROM CMOS – MARKET DYNAMICS

Contract manufacturing organisations have experienced a good deal of success in recent years. However, a pure CMO model is no longer effective in solving many of the pharmaceutical industry’s challenges, and successful companies have evolved into solution providers.

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Two key factors are driving increased focus in solution provider business models. First, the introduction of innovative medicines has slowed in the branded pharmaceutical industry over the past decade, leading to significant generic erosion and pressure on innovator company revenues and profit margins. At the same time, the level of competition has increased. Companies of all sizes are under pressure to differentiate their products – not only to convince regulators and clinicians of a drug’s superiority, but also to ensure that payers are willing to reimburse.

These market dynamics are driving companies to strive to achieve improved therapeutic profiles earlier in development in order to maximise their return on investments. In many cases, the use of full solutions providers can assist them in achieving this goal.

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SOLUBILITY ENHANCEMENT: A CASE STUDY IN MEETING CUSTOMER NEEDS

One challenge where this is very evident is in the need to optimise the bioavailability of compounds, with respect to solubility enhancement. Estimates have varied over the years, but at least 40% and as many as 70% of new chemical entities are considered poorly soluble in water, leading to low bioavailability, high intra- and inter-patient response variability, and variable dose proportionality. When BCS Class II (high permeability, low solubility) and BCS Class IV (low permeability, low solubility) are combined, the percentage of poorly soluble NCEs is approximately 90%. Amongst approved drugs, 30% are considered poorly soluble. Comparing the percentage for drugs in development with that for approved drugs shows a clear trend towards the development of an increasing number of molecules with poor solubility.

BCS Classification of new molecular entities in development is shown in Figure 1. The number of molecules on market that might benefit from further differentiation is significant. Moreover, the number of compounds in development that become shelved or are launched with suboptimal product profiles as a result of low solubility represents a very large lost opportunity for pharmaceutical industry investment.

SOLUBILITY ENHANCEMENT IS MULTI-FACTORIAL - UNDERSTANDING THE FACTORS:

Solubility, and thus bioavailability, can be enhanced in four main ways:
1. Optimising the API form itself
2. Optimising the Formulation
3. Optimising the Processing
4. Optimising the Dose Delivery

On many occasions, optimising solubility requires iterations across the above four factors.

Catalent has recently invested, both internally and in the form of alliances, to deliver a complete solution across these parameters, without clients having to deal with time- and resource-constraining discussions across multiple companies or teams.

THE EVOLVED SOLUTION MODEL

As a complete solution model solving bioavailability, Catalent expanded its reach in both technology offerings and scientific expertise to provide clients with a single, integrated partner. Following are the innovative building blocks that Catalent offers to address the four main factors mentioned above and best meet the needs of the pharmaceutical industry customers.

1. Optimising the API itself
Catalent offers OptiForm salt screening to optimise molecule form selection and maximise solubility potential. Additional clinical, analytical, supplies, and packaging services expedite trials.

2. Optimising formulation
Catalent has expert formulation scientists who have helped bring molecules from lab to market for 90 of the top 100 pharmaceutical companies, 44 of the top 50 biotech firms, and hundreds of smaller innovators. Catalent offers RP Scherer Softgel and OptiShell, a bovine based capsule, both of which are optimal for lipid formulations.

3. Optimising the process
For solid dispersions, RP Scherer is the industry leader, with 75 years of experience addressing solubility issues. Understanding that hot melt extrusion is an additional solution for solid dispersions for certain molecules, Catalent has expanded to offer OptiMelt hot melt extrusion pilot, lab, and commercial capabilities in a global footprint.

COMBINING WORLD-LEADING TECHNICAL EXPERTISE

For a complete solution offering for solubility enhancement, Catalent needed to offer raw ingredient solubilisers and excipients. However, this was a missing component. Therefore, in April 2012, realising a mutual combined benefit to customers for solving the same need, BASF and Catalent entered into an innovative open alliance to fill this gap.

The fact that the companies entered into an open alliance means that they collaborate in cases where it serves their customers best, but would liaise with someone else with a more tailored offering for a specific customer need or at a customer request. The main rationale for this open alliance can be summarised as follows:
• Provides customers with a unique range of seamless solutions
• Complementary offerings to enhance solubility and permeability
• A full solution for development - from molecule to market

IN APRIL 2012, REALISING A MUTUAL COMBINED BENEFIT TO CUSTOMERS FOR SOLVING THE SAME NEED, BASF AND CATALENT ENTERED INTO AN INNOVATIVE OPEN ALLIANCE
The combined solubility enhancement capabilities from the BASF-Catalent open alliance are shown in Figure 2.

4. Optimising the Dose Delivery Form

Selection of the appropriate dose delivery form provides a variety of options to enhance bioavailability and solubility. Catalent has offered RP Scherer Softgel and the most advanced controlled release capabilities to the market for decades, including a complete range of granulation, tablet, capsule, bead and also coating options. Wurster fluid bed technology is also available in both the US and Europe to produce desired release profiles.

Catalent has also launched OSDRC® OptiDose™ optimised dosage technology to advance innovation in controlled release. This novel delivery technology enables the design of single or multi-core tablets, with a variety of core numbers, shapes, sizes and placement within the tablet, offering the broadest range of controlled release designs for drug formulators in a one-step, solvent-free manufacturing process.

The flexibility of OSDRC® OptiDose™ controlled release formulations is able to improve therapeutic profiles to meet a variety of patient needs, including:
- Control API plasma release profiles
- Improve target delivery
- Optimise patient dosing
- Enhance patient convenience

A final offering that Catalent includes in its comprehensive bioavailability solution technologies is its Zydus® platform, including Zydus® ODT (orally disintegrating tablets), Zydus® stick packs, and Zydus® nano. For some APIs, an ODT can be absorbed buccally (through the oral mucosa) and lead to increased bioavailability and/or improved safety profiles by greatly avoiding first-pass metabolite formation.

This was the case when Catalent partnered with Valeant Pharmaceuticals (Montreal, Canada) to develop Zelapar®, a formulation of selegiline for Parkinson’s Disease, using Zydus® ODT. The improved therapeutic profile of the Zydus® ODT formulation is shown in Figure 3.

An additional benefit from the improved product profile achieved by using Zydus® ODT to formulate Zelapar®, beyond increased bioavailability and improved safety profile, was a significant increase in patient medication compliance. This was demonstrated in a longitudinal one-year, blinded, patient-record-analysis study, which compared the compliance rates for the standard pill and Zelapar®. In US Medicare patients, a compliance rate of 98.5% was achieved with Zelapar®, compared with 81% with the standard oral tablet. This data, and data from other cohorts, is shown in Figure 4.

CONCLUSION

The global pharmaceutical industry has faced unprecedented challenges, because of a reduced number of innovative drugs, increased competition, and heightened pressures from regulators and payers. These dynamics have increased the need to maximise product differentiation not only as part of lifecycle manage-
ment strategies, but early in the development process as well. This has led to the need for CMOs to adapt and modify both their technology offerings and their business models. The historic model of a pure CMO is not viable if the evolved needs of the pharmaceutical industry are to be met. True solution providers will be required in the future to help solve the current challenges facing our industry.

Catalent has already adapted to these changing industry needs by understanding that solubility plus equipment is not the answer. A true partnership with expert scientists able to bridge the integrated complexities from molecule to market with the best technologies and partnerships is the way of the future to deliver better treatments to our customers and – most importantly – to the patients who will ultimately benefit.

REFERENCES


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