Reformulation

Embracing Formulation Expertise to Extend Exclusivity & Improve the Patient Experience

By Syed T. Husain, Alcami

Offering potential exclusivity and access to larger markets, reformulation efforts can prove extremely valuable to both pharmaceutical and biopharmaceutical manufacturers. With reliable CDMO support, this value can be developed in a cost-effective manner and with minimal inconvenience, while reducing the impact of patent loss.

With considerable room for growth in emerging markets, the surge in biopharmaceutical drug development and approvals, as well as merger and acquisition activities that are helping to further existing expertise, has left the pharmaceuticals market poised for growth. At an expected compounded annual growth rate (CAGR) of 4% to 7%, the market is predicted to reach $1.3 trillion in 2018, but challenges still exist as traditional pharmaceuticals are rapidly approaching or have already reached the patent cliff and biopharmaceuticals are beginning to experience competition from biosimilars.[1] Faced with these challenges, manufacturers must look for new, innovative ways to maintain and/or grow their market share and remain relevant.

One of the primary strategies for surviving the patent cliff is to stretch existing product lines by reformulating already approved and patented medications. While reformulation can prove to be a cost-effective method of extending patent protection, the process itself can also be complex and expensive and isn't always successful. To apply for an extension of market exclusivity, the reformulated drug must not only meet all criteria aimed at protecting patients, but the new substance must also improve upon the original purpose of the drug.[2] Due to the inherent complexities and the FDA regulations involved, many companies are strategically engaging contract development and manufacturing organizations (CDMOs) as a way of harnessing existing expertise and simplifying the process.

Alcami, the alliance created by the joining of AAIPharma Services and Cambridge Major Laboratories, is one such CDMO. Following the 2013 alliance,

Alcami became a leading provider of integrated chemistry, manufacturing and controls (CMC) services across both drug substance and drug product. Many manufacturers aim to reformulate the active ingredients in a given drug, enough to be able to offer new benefits, while still being able to use previous clinical trials when submitting a new drug application (NDA), but this is often a complex task.3 With the current trend towards outsourcing in this space, leading companies like Alcami are able to further bolster formulation expertise while providing expert development and prototype services. The benefits of engaging a CDMO partner with a reliable life cycle management (LCM) strategy during reformulation development are invaluable.

New Delivery Options To Delay The Cliff And Capture The Market

Many reformulation strategies have objectives that are both commercial and technical.[4] The technical objectives, including improving/removing the taste, decreasing the physical size of a solid dose or simply making the medication more convenient by offering it in a different form, often highlight the commercial objectives (targeting a previously unavailable section of the market, improving brand perception, etc.).[4] However, all of these objectives must be met while using existing clinical trial data for the new approval.

Reformulating a pharmaceutical drug to extend data exclusivity can involve alterations to its molecular entity (a method that has been used successfully for metabolites, enantiomers and polymorphs), creating new delivery options or developing a new indication (which can quickly become cost prohibitive), each of which has the potential to improve an existing drug and create broader patient interest.3 However, new delivery options — dosage forms or routes of administration — are especially appealing because they can allow a drug manufacturer to expand its offerings in a given market while targeting a new, potentially larger demographic that may not have been able to use the medication in its original dosage form. The most popular dosing change involves the development of modified release — including controlled or extended release (XR) and fixed-dose combination (FDC) — versions of the patented drug.[3] In fact, XR formulations have proven so valuable that some manufacturers begin development even before the original formulation of the drug has been approved.[2]

In addition to meeting many technical and commercial objectives, XR medications are often ideal for patients because the new dosage form can provide improved pharmacokinetic profiles.4 By regulating the release of the active pharmaceutical ingredient (API), XR medications extend the duration of

the therapeutic effect, while potentially minimizing the occurrence of adverse effects, by maintaining the concentration of the drug and avoiding exposing the patient to potentially toxic drug levels.[4] Additionally, controlled release medications can help increase drug compliance and patient convenience by reducing the dosing requirements that might be associated with the standard release version of the drug.

Similarly, FDCs may be a viable option, as they can combine already approved actives into one drug or allow for the precise release of a given active ingredient (e.g., combining an immediate release and a controlled release in a single dose). With all of these potential considerations, it's easy to understand why, according to the 2016 Nice Insight CDMO Outsourcing Survey, 57% of respondents reported outsourcing pre-formulation/formulation services to CDMO partners and 63% reported outsourcing the development of controlled release formulations.5 CDMO expertise can help create the formulation necessary for modified-release drugs that use various drug-delivery technologies in addition to the now common oral delivery, including products such as implants, suppositories, injectables, inhalants, or those involving ocular or transdermal delivery systems.[2]

As a leading CDMO, Alcami has extensive capabilities and capacity to provide analytical testing, development, prototyping and reformulation services for APIs with both oral solid and parenteral dose finished products. Providing an integrated offering for both drug substance and drug product at every development stage, beginning with solid state chemistry and formulation development, Alcami has worked to create a robust new outsourcing offering to assist with developments in this space, allowing the patent holder to benefit from additional, potentially significant, protection.

The introduction of the ProForm Select offering built on their centers of excellence in Solid State Chemistry, Process Chemistry, and Formulation Development also sets Alcami apart in the space. Ideal program candidates are small molecule solid oral dosage crystalline and amorphous drug products, with an Occupational Exposure Limit (OEL) as low as 1mg/m3. Throughout all phases, from concept to clinical, commercial level control and post commercial/secondary supply, ProForm Select aids in timeline reduction and parallel focus on drug substance and drug product. The ProForm Select program integrates API and Drug Product solutions from characterization, supply chain support to technical and risk assessment (See Fig 1.)

By submitting a small-molecule drug application through the 505(b)(2) approval pathway, pharmaceutical manufacturers can introduce modest changes or reformulations to an existing drug as a way of receiving additional market exclusivity for up to seven years.[2] When the new drug formulation is approved, the manufacturer can also discontinue marketing the old formulation and have the listing removed from the Orange Book — preventing an abbreviated new drug application (ANDA) from referencing the old drug in the future — but discontinuation is not required.[3] For most new drug approvals, data exclusivity, including dosage form and use exclusivity, can be obtained, preventing the FDA from approving ANDAs for three years. Orphan drug exclusivity is also available and can extend all market exclusivity by seven years, while pediatric exclusivity can only extend the term of regulatory exclusivity of all Orange Book listed patents for an additional six months.[3]

Unique Considerations For Biopharmaceutical Reformulations

As biosimilars begin to enter the market, reformulation can seem appealing. However, the regulations surrounding the development of biopharmaceuticals and biosimilars, as well as the restrictions placed on data exclusivity for these products, are different from those regulating small molecule development.[3] An exclusivity period of 12 years is granted to new biologic products, but the FDA will not extend exclusivity for new dosage forms, routes of administration, or dosing schedules. When seeking an extension of exclusivity for a biopharmaceutical drug, formulation and delivery device changes are allowed provided they don't create a clinically significant difference, but structural changes that alter the safety, purity, or potency are the only path for manufacturers; however, under 42 U.S.C. § 262(m), pediatric exclusivity can extend the original exclusivity period by six months.[3]

According to the 2016 Nice Insight CDMO Outsourcing Survey, the appeal of outsourcing in the area of biopharmaceuticals is also significant, with 53% of respondents outsourcing to CDMOs who can provide bioavailability enhancing excipients.5 With aseptic processing and services to improve safety, purity and potency, full service CDMOs such as Alcami can ease the process of navigating this space. After announcing significant investments in additional capabilities for parenteral fill-finish, including additional sterile lines and lyophilization capacity, Alcami is highly specialized for handling biopharmaceuticals and can prove beneficial when exclusivity extensions are part of the life cycle management (LCM) strategy for these products.

By offering additional exclusivity and the potential of a larger market, reformulation efforts can prove exceptionally valuable to both pharmaceutical and biopharmaceutical manufacturers. With a reliable CDMO partner, this value can often be recognized with minimal cost and inconvenience while reducing the cliff to more of a gradual slope that can help a manufacturer improve its brand and the lives of the patients it serves.

Figure 1
Key Benefits of Proform Select™ Program

Integration
A single solution provider for AP and Drug Product development, with seamless quality and technical alignment.

Attention
Cross-functional project management, pro-viding one point of contact for you and supporting technical alignment and cross- functional coordination.

Speed
RFP to program commencement in less than a month. A single contract and project team for the entire program contributes to timeline compression by eliminating hand-off time, and parallel activities create further efficiencies.

Ease of Use
ProForm Select™ aligns our solid-state and formulation development groups to design an efficient, robust and competitive appro-ach to take your API to its finished dosage form. An early selection profile is established to mitigate risk in form variation and development, resulting in a scalable, targeted-to-dosage form.

API Solutions
- Appropriate salt selection
  - » Crystal consistency
  - » Polymorph selectivity
  - » Reproducible API
- Robust process chemistry
  - » Clinical: Specify and define critical quality attributes
  - » Commercial: Specify and measure critical quality attributes
- Commercial consistency with raw material an manufacturing equipment changes

• Second Supplier Qualification

Drug Product Solutions

• Dissolution profile
• Bioavailability
• Stability and impurity profile consistency
• Consistent solubility
• Robust formulation process
• Robust manufacturing process
    » Clinical: Specify and define critical quality attributes
    » Commercial: Specify and measure critical quality attributes
• Commercial consistency with raw material and manufacturing equipment changes
• Second Supplier Qualification

Callout

By submitting a small-molecule drug application through the 505(b)(2) approval pathway, pharmaceutical manufacturers can introduce modest changes or reformulations to an existing drug as a way of receiving additional market exclusivity for up to seven years.

References

1. Global Outlook for Medicines Through 2018. Rep. IMS Health. Nov. 2014. Web.
2. Wright, Peggy. "Modified Release Formulations Give New Life to Drugs." Pharmaceutical Commerce. 28 Apr. 2014. Web.
3. Steffe, Eric K., Bonnie Nannenga-Combs, and Gaby L. Longsworth. "The Impact Of Reformulation Strategies On Pharmaceuticals, Biologics." Biosimilar Development. 14 Mar. 2016. Web.
4. Siew, Adeline. "Stretching Product Value through Reformulation Strategies." Pharmaceutical Technology. 2 Oct. 2015. Web.
5. The 2016 Nice Insight Contract Development & Manufacturing Survey. Syed T. Husain Chief Commercial Officer, Alcami

About The Author

Syed Husain, the commercial leader for Alcami, leverages in-depth experience in sales, business development, marketing and operations for the development and manufacture of small molecules, antibody drug conjugates (ADCs), peptides, and large molecules covering drug substance and drug product. Syed earned a BS in chemical engineering from New Jersey Institute of Technology in 2003 and an MBA from Cornell University in 2009.

LinkedIn www.linkedin.com/in/syedthusain
Email syed.husain@alcaminow.com