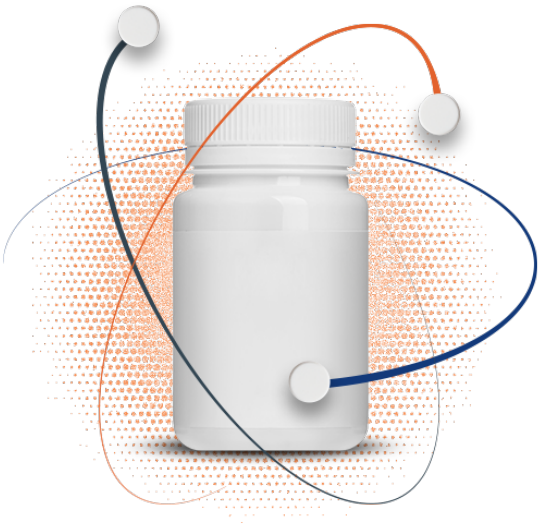
APRECIA®
THE 3DP PHARMACEUTICAL COMPANY

First FDA Approved 3D Printed Drug Paved

New Path For Increased Precision In Patient Care

The growth of the pharmaceutical industry and its willingness to explore novel strategies in drug development and delivery is reshaping the industry and renewing interest in how to optimize therapies and increase precision in patient care. Specifically, innovations in science and technology are creating exciting opportunities to treat rare diseases and advance personalized medicine. However, traditional methods for development and manufacturing do not offer the efficiency and speed needed to keep pace with this evolution. In addition, rising brand and generic competition is adding to market pressures, as pharmaceutical manufacturers must seek approaches that address patient needs in more unique ways. These reasons are why it is critical that the industry explores other methods to maximize productivity and improve the patient experience.

In 2015, the approval of the epilepsy treatment Spritam created a potential avenue for doing so as it was the first prescription drug manufactured using 3D printing (3DP). 3DP, known as additive manufacturing, is ideal for pharmaceuticals because it offers enhanced precision in developing and formulating dosage forms. This presents a number of potential benefits for developing personalized medicines. Some examples include creating different dosage strengths to reduce pill burden or shapes of dosage forms to improve absorption or increasing compliance through faster dissolution, modified release profiles, and/or combination products.



These advantages allow drug companies to not only boost efficacy and adherence but also contribute to their brand longevity by expanding and capturing market share with other dosage form options. Through this breakthrough method of manufacturing and its fast-melt capabilities, there is an ability to overcome several obstacles, thereby contributing to better patient outcomes in the solid dose market.

The Reality Of Dysphagia: Can The Solid Dose Market Afford To Overlook It?

ZipDose, the formulation platform used to manufacture Spritam, is a 3DP technology that uses an aqueous fluid to bind together multiple layers of powder, which can rapidly disintegrate on contact with liquid. As with any tablet manufacturing process, the pharmaceutical powder is a blend of an active pharmaceutical ingredient (API) and its excipient. In the ZipDose manufacturing process, the powder is dispensed onto a

forming area and then run underneath a print head that deposits a specific pattern of liquid. The design of the dosage form is preprogrammed using a digital print image that varies from product to product. The build process is considered complete once the steps of powder dispensing and liquid depositing have been repeated a product-specific number of times. Essentially, the ZipDose process stacks the layers of powder and stitches them together with a binding fluid. The result is a very porous dosage form that collapses once a small amount of liquid touches it.

Although other fast-melt technology platforms existed prior to ZipDose, 94 percent of dosage strengths made with these manufacturing technologies and approved in the United States had a dose ceiling of 50 milligrams (mgs) of API.[1] The highest strength ever approved before Spritam was 275 mgs. While it is possible to formulate tablets above 50 mgs with conventional fast-melt technology platforms, those formulations do not always disintegrate rapidly and tend to leave a gritty feeling in the patient's mouth due to the amount of API and excipients used. As a result, there is limited commercial appeal for patients suffering from dysphagia, a medical term used to describe a difficulty swallowing. Dysphagia is most commonly linked to children and the elderly, yet a recent national survey estimated that over 40 percent of adults in the general community experience problems swallowing pills.[2] The impact on compliance becomes apparent, as 14 percent of adults with this condition reported they delay taking their medication because of the issue, with 8 percent of adults skipping a dose altogether.

Another study found that out of 2,000 patients surveyed in the U.S. and Germany, over half were unable to swallow traditional tablets and/or capsules.[3] Of the participants, 44 percent of those 65 and older reported issues with dysphagia; however, 70 percent of those 16 to 34 also reported the same problem. ZipDose offers a solution to those suffering from dysphagia, as up to 1,000 mgs of drug formulated with ZipDose can be quickly and successfully disintegrated with just a "sip" of liquid. Masking the bitter flavor of high-dose medications is another hurdle that had to be overcome, which ZipDose is able to do using a variety of taste-masking technologies.

For any pharmaceutical company targeting the solid dose market, dysphagia is a major obstacle it must address for its product to have a positive effect on patient treatment. Aprecia Pharmaceuticals, the company that developed ZipDose and Spritam, recognized the opportunity it had to introduce a solution that could unlock the true potential of 3DP for pharmaceuticals. First though, the team at Aprecia wanted to identify a candidate that could show the value proposition of a successful fast-melt technology.

ZipDose And The Treatment Of Epilepsy

To determine where ZipDose could have the most impact, it was important to understand the disease states and patient subsets where dysphagia was a significant burden to effective treatment. Aprecia's research began with looking at claims data and the accompanying diagnostic codes for dysphagia. This information revealed that not only was the incidence of dysphagia high in children and the elderly with epilepsy, but of the claims reviewed, one in five adults with epilepsy had dysphagia. Overall, the finding indicated dysphagia was a problem for all age groups with epilepsy.

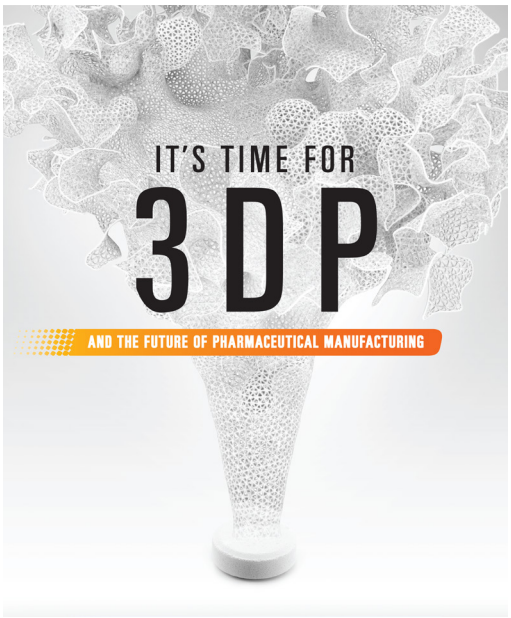
Persistence with taking a medicine is critical for any disease, but those with epilepsy are at a high risk for breakthrough seizures. A major reason they experience these seizures is because they are not compliant with their medication. This lack of adherence can have a substantial socioeconomic impact, as those experiencing breakthrough seizures can frequently end up in the emergency room and also lose their driver's license, resulting in an inability to work and/or support themselves. There are often other comorbidities with epilepsy, such as stroke, Alzheimer's disease, and depression, as well as comorbidities with developmental and intellectual disabilities, including head trauma and neck tumors. Patients experiencing these additional issues often require the help of a caregiver to oversee their regimen, increasing the need for something easier for another person to administer to a patient. For children specifically, medication is usually given in a liquid form, due to either age or convenience. Yet, liquids can be difficult to administer to younger

patients, and giving an exact measurement is similarly challenging.

Aprecia also considered the current standard of care for epilepsy patients, which involves identifying an appropriate drug treatment or treatment combination, with patients taking first-, second-, and third-generation drugs to determine what works best for them. These anti-epilepsy drugs are typically administered in high drug loads and, for the products of most interest to Aprecia, there was not an orally disintegrating tablet available. One epilepsy medication in particular, levetiracetam, had four tablet strengths: 250 mgs, 500 mgs, 750 mgs, and 1,000 mgs. It also had a bitter taste, which required masking. These factors made levetiracetam an optimal candidate for demonstrating the ZipDose value proposition relative to fast-melt formulations. The next step was to collaborate with the FDA on how to bring levetiracetam's new dosage form to market.

Spritam's Regulatory Journey

Pharma's reputation for being averse to change often traces back to the struggles associated with regulatory approval. While presenting the FDA with a breakthrough manufacturing method, such as 3DP, might seem intimidating, Spritam's approval was facilitated through the 505(b)(2) regulatory pathway. This hybrid of a New Drug Application (NDA) and Abbreviated New Drug Application (ANDA) offers three to five years of market exclusivity for a follow-on product provided new clinical data accompanies the application. At minimum, the 505(b)(2) application for a new dosage form requires 12 months of stability data and a bioavailability/bioequivalence (BA/BE) study, followed by a 10-month review process. Therefore, if the development of a 505(b)(2) product candidate is initiated five years before the earliest possible generic launch, there should be ample time to develop the new formulation. Even if it took a full year to lock in the final formulation, that still leaves two years on the market for the drug to address patient needs and capture market share for the new dosage form.



For Spritam, Aprecia used safety and efficacy data on file with the FDA to support labeling claims and a BA/BE study to prove bioequivalence to the reference drug Keppra (trade name for levetiracetam), paving a way for it to make it to market faster and more efficiently. Therefore, by changing the formulation of a drug using ZipDose 3DP, a drug manufacturer gains another option when considering a life cycle management strategy and, potentially, a unique advantage in its market, especially if a product could work for an indication where the patient would benefit from a fast-melting ZipDose formulation. Nonetheless, even though the 505(b)(2) pathway provides a more efficient and expedited route to market, thinking bigger about market share early in the process allows a company to add more than just a new dosage form. Planning a line extension of your brand at least five years prior to loss of exclusivity could sustain your market standing and lengthen the life of your product. Clinical studies can be expensive and time-consuming, so including all potential indications and dosage forms in the beginning could prevent extra costs and delays later when the realization occurs that a product has more potential than originally considered.

Before gaining approval of Spritam, Aprecia conducted several "lunch-and-learns" that included a broad audience from various departments and disciplines across the FDA to learn more about 3DP and how it applied to pharmaceutical manufacturing. It also held two Type B meetings with the FDA and hosted multiple visits to its launch facility, so regulators could tour and see the 3DP manufacturing process and equipment. This constructive and collaborative process gave the FDA the insight it needed to better

understand 3DP prior to approval. The interactions also gave both sides the opportunity to work through other challenges, such as what the dosage form designation for ZipDose should be. Aprecia consulted with not just the FDA but also the United States Pharmacopeia (USP) to agree on a dosage form designation that is not substitutable for a generic when it comes to reimbursement and pharmacy distribution.

3DP And The Future Of Patient-Centric Dosage Forms

The approval of Spritam validated a commercial process for 3DP drugs under FDA regulation, opening the door to a wide range of therapeutic options a pharma manufacturer could achieve using 3DP for pharmaceuticals. Beyond fast-melt technology, 3DP formulation flexibility allows expansion into other platforms, including fixed-dose combination products, multiple release profiles, and buccal/sublingual delivery. It is not difficult to imagine that, one day, a truly personalized dose could be custom printed for a patient to meet his or her exact requirements. The revolutionary 3DP technology is an avenue for drug development creating new possibilities at the forefront of modern medicine, where science and innovation are partnering to lower the cost of manufacturing, increase efficacy, and ultimately transform patient care.

1. Based on internal research using the 2016 FDA Orange Book

2. Carnaby-Mann, Giselle & Crary, Michael, JAMA Network, Pill Swallowing By Adults With Dysphagia — https://jamanetwork.com/journals/jamaotolaryngology/fullarticle/649710

3. Hein, Thomas, Hermes Pharma, A Hard Pill To Swallow: Meeting The Needs of Modern Consumers — http://ipimediaworld.com/wp-content/uploads/2014/12/A-hard-pill....pdf