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OSD: Strong and steady

The oral solid dose sector had a successful 2019 and may see further vigor in the near future

By Karen Langhauser, Chief Content Director

Oral solid dose formulations are the pharma industry's tried-and-true treatment forms.

Tablets and capsules are efficient and cost-effective to manufacture, shelf stable and easy to administer. They are widely understood and embraced by patients worldwide.

Despite billion-dollar large molecule injectable drugs like Humira and Keytruda topping the market charts and a pipeline buzzing with excitement over biologic hopefuls using novel scientific approaches such as CAR-T cell therapy, small molecule solid dose drugs still make up the vast majority of drugs on the U.S. market.

And, for the past two years, new drug approval for tablets and capsules specifically have outstripped approvals for injectables, solutions and creams.

Adding to this, several small molecule OSD products are beginning to show promise in the fight against COVID-19, thrusting aging medications back into the spotlight and renewing patients' and manufacturers' enthusiasm for OSD drugs.

NEW DRUG APPROVALS

When it comes to novel drug approvals, oral solid dose products continue to lead the charts. In 2019, the U.S. Food and Drug Administration's (FDA) Center for Drug Evaluation and Research (CDER) approved

48 novel drugs. OSD products accounted 54 percent of these new FDA-approved drugs. Of the 26 newly approved OSD products, 19 are tablets and seven are capsules.

This is the highest percentage of OSD approvals seen since 2013.

CDER identified 20 of the 48 novel drugs approved in 2019 as "first-in-class" — drugs that use a new and unique mechanism of action for treating medical conditions. Ten of these innovative drugs were OSD products. One notable approval was Janssen Pharmaceutical's Balversa (erdafitinib) tablets, approved under the FDA's accelerated approval program in April 2019 as a treatment for adult patients with locally advanced or metastatic bladder cancer. The first FGFR kinase inhibitor to receive FDA approval, Balversa is an important new therapy for a small subset of patients with urothelial carcinoma who, up until this approval, had limited treatment options.

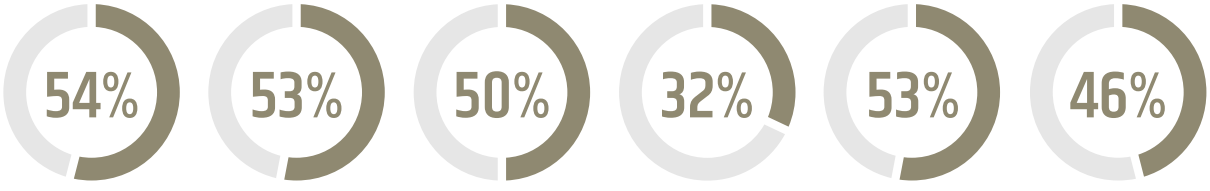
Novartis topped the oral solid dose approval chart in 2019 with three novel drug approvals. These approvals included: Egaten tablets (Feb. 2019) to treat Fasciolasis, a neglected tropical disease; Mayzent tablets (March 2019) to treat adults with relapsing forms of multiple sclerosis; and Piqray tablets (May 2019), a targeted treatment for advanced breast cancer.

The FDA also approved a total of 1,171 generic drugs in 2019 — an all-time record. Importantly, 107 of these approvals were "first generics" — meaning the manufacturers were the first to get approval to launch generic equivalents. Close to 60 percent of these first generics were OSD products.

MARKET MOVES

GlaxoSmithKline kicked off 2019 by

OSD percentage of novel drug approvals



2019	2018	2017	2016	2015	2014
26 of 48 drugs were solid dose products: 19 tablets, 7 capsules	31 of 59 drugs were solid dose products: 24 tablets, 7 capsules	23 of 46 drugs were solid dose products: 17 tablets, 5 capsules	7 of 22 drugs were solid dose products: 7 tablets	24 of 45 drugs were solid dose products: 15 tablets, 9 capsules	19 of 41 drugs were solid dose products: 10 tablets, 9 capsules

*INFORMATION COURTESY OF US FDA

completing a $5.1 billion acquisition of Tesaro, an oncology-focused company based in Waltham, Massachusetts. Driving the deal was Tesaro's biggest product, Zejula capsules, oral poly ADP ribose polymerase inhibitors approved for use in ovarian cancer.

Last summer, Novo Nordisk bought a state-of-the-art manufacturing plant for solid oral dose product from Purdue Pharma. The North Carolina facility enabled Novo to establish tablet production capacity in the U.S. in order to build a domestic supply chain for its oral semaglutide, the first glucagon-like peptide-1 (GLP-1) receptor agonist available in a pill form.

Around the time same, Amgen paid Celgene $13.4 billion for the rights to Otezla (apremilast) tablets. The tablets are the only oral, non-biologic treatment for psoriasis and psoriatic arthritis — ailments normally treated via injection or creams.

In recent news, India's Piramal Pharma Solutions announced that the CDMO will acquire a solid oral dosage drug product manufacturing facility located in Sellersville, Penn. from G&W Laboratories. This acquisition is important because it gives Piramal solid oral dosage form capabilities in North America.

RECALLS

Oral solid dose products had their share of struggles in 2019 as well. A series of recalls from 2018 spilled over into 2019 after regulators found several different toxic chemicals in the commonly used "sartan" blood pressure tablets — valsartan, losartan and irbesartan. Multiple drugmakers initiated recalls of tablets found to be contaminated with NDMA, NMBA or NDEA — all potentially cancer-causing chemicals.

This was followed by a mass recall of Zantac and generic Zantac (ranitidine) capsules and tablets because of confirmed contamination with NDMA above levels established by the FDA.

The bulk of the contamination in both scenarios was traced back to active pharmaceutical ingredients (APIs) being sourced from specific factories in China. In the case of Zantac, testing determined that levels of NDMA increased over time depending on how the ranitidine was stored.

2019 brought the greatest percentage of OSD drug approvals since 2013.

The contamination was part of what has emerged as a much larger issue — the U.S.'s dependence on pharma ingredients made in China — that has gotten heightened attention during the coronavirus pandemic.

FIGHTING COVID-19

The pandemic drove non-COVID patients, fearing possible infection, out of clinical settings, which made administering drugs with complicated delivery methods difficult, if not impossible — again highlighting an important advantage of easy-to-use OSD products.

Adding to that, while most of the world's attention is focused on developing possible SARS-CoV-2 vaccines, numerous OSD products have begun to share the spotlight as promising treatments for the symptoms of COVID-19.

Small molecule oral solid dose products, such as hydroxychloroquine (used in malaria and lupus treatment), chloroquine (used in malaria treatment), azithromycin (informally known as a Z-pak), lopinavir/ritonavir combos (used in HIV treatment) and colchicine (used in gout treatment) continue to be tested as possible COVID-19 treatments.

Given the scope of COVID-19 infections, ease of manufacturing, distribution and administration of tablets and capsules add to their attractiveness as potential treatments. But because some of these medications are decades old, and have previously been used for rare indications, most have only been produced in smaller batches — so if proven to be effective against COVID-19, manufacturers will need to reconfigure their production for large-scale output.

According to a blog post by solid dose expert, Dave DiProspero, director of Pharmaceutical Process Technology at CRB, this potential surge in demand "could hail a long-term shift for OSD manufacturers."

"By taking decisive action to upgrade and expand their operations, OSD manufacturers will position themselves to play a key role in defeating both today's pandemic and whatever unseen health threats the future may hold," said DiProspero.

Oral solid dose products continue to play a pivotal role in the industry's quest to produce quality, effective treatments for myriad diseases. And, now at the mid-point of 2020, just over half of the novel drug approvals are OSD products — signaling there is even more innovation to come.

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Beyond the surface

For pharma, the omega-3 fatty acid waters could run deep

By Karen Langhauser, Chief Content Director

For years, the prescription omega-3 waters have appeared calm. While other industries are reaping the benefits of the $44 billion global omega-3 finished product market, pharma has yet to fully jump in.

On the surface, pharma applications are limited. There are just four branded drugs approved by the U.S. Food and Drug Administration with omega-3 fatty acids as active ingredients, and only two of those drugs (Lovaza and Vascepa) are commercially available in the U.S. Until recently, all approvals were restricted to the same niche patient population — adults with severely high triglyceride levels.

Yet, within the pharma industry, the waters are starting to ripple. In late 2019, Amarin's Vascepa approval was expanded, making it the first and only drug approved to reduce

$44.2 billion: Size of the EPA and DHA omega-3 finished product market in 2019.

—GOED 2020 Global EPA & DHA Finished Products Report

cardiovascular risk among patients with elevated triglyceride levels — and greatly widening the treatment population.

But the most intriguing part of pharma's omega-3 story may be what is churning right beneath the surface.

The Global Organization for EPA and DHA Omega-3s (GOED), currently in the final stages of creating a massive searchable clinical study database, reports that there are more than 42,000 published studies on EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid) — including more than 4,000 human clinical trials.

Adam Ismail, who has spent over 20 years working in the omega-3 space, and is now serving as chief strategy officer for KD Pharma Group, recently identified 88 drugs in pharma's preclinical and clinical pipeline that use EPA, DHA or derivatives.

Pharma's "deep and extensive omega-3 pipelines," says Ismail, "reach far beyond the cardiovascular space."

Among the pipeline treatments is an orphan drug being jointly developed by KD Biopharma and SLA Pharma, currently in phase 3 trials for a rare hereditary condition that leads to colorectal cancer. That same medicine, along with a handful of other omega-3 drugs, is also being explored as a COVID-19 treatment. Additional trials evaluating omega-3 drugs as treatments and preventatives for mental health and depression, gastrointestinal diseases, eye diseases and rare genetic disorders are underway.

As pharma continues to test the waters, the clinical and financial significance of omega-3 treatments is becoming too compelling to ignore.

HOW MANY FISH IN THE SEA?

Omega-3s are a family of polyunsaturated fats (commonly referred to as "fish oils") that the human body needs but cannot manufacture on its own. Among these critical fatty acids are two sought-after acids — EPA and DHA — which can be found in a variety of sources, including fatty or oily fish, fish body or liver oils, marine crustaceans, marine microorganisms, or even genetically modified terrestrial plants.

According to GOED, suppliers produced 111,210 metric tons of EPA and DHA omega-3 ingredients in 2018. The pharma industry takes just a small percentage of these ingredients, with the majority going to dietary supplements. Aldo Bernasconi, vice president of data science for GOED, estimates that currently, pharma only buys about 2 percent of the ingredient volume, but because pharma utilizes very highly concentrated, often pricier fish oils, pharma's spend makes up about 13 percent of the total ingredient value.

Of the four FDA-approved drugs, three contain a mixture of EPA and DHA — two use the combo in ethyl ester form and the third (Epanova) contains the mixture as free fatty acids to aid bioavailability. Amarin's Vascepa is made up of one active ingredient: icosapent ethyl, which is a form of EPA.

While research strongly supports the body's need for both DHA and EPA, EPA oils tend to be less common and increasingly sought after by industries, pharma included.

"One complication is that fish have more DHA than EPA, so if you are going to produce a high concentration EPA drug, then you need to start from fish oil particularly high in EPA, and that type of oil is limited," explains Bernasconi.

Anchovies from Morocco and Peru tend to be high in EPA. But the composition of fish is dependent upon various factors. "Fish are complicated and composition of the oils in them changes with environmental conditions such as water temperature and diet," says Bernasconi.

"Lately, fisheries have been producing a little bit less EPA than traditionally — we will see if that changes over time. But it is a natural resource so you are somewhat dependent on what happens in the oceans," says Ismail.

FDA-approved omega-3 drugs

Lovaza/Omacor

Approved: 2004 Launched: 2005

Developed by: Pronova BioPharma

Rights: Marketed by GlaxoSmithKline

Capsules are a combination of ethyl esters of omega-3 fatty acids, principally EPA and DHA

Epanova

Approved: 2014 Never launched

Developed by: Omthera Pharmaceuticals

Rights: Omthera is a wholly-owned subsidiary of AstraZeneca

Capsules are a combination of principally EPA and DHA in free fatty acid form

Omtryg

Approved: 2014 Never launched

Developed by: Trygg Pharma

Rights: Owned (and discontinued) by Osmotica Pharmaceuticals

Capsules are a combination of ethyl esters of omega-3 fatty acids, principally EPA and DHA

Vascepa

Approved: 2013/Expanded approval 2019

Launched: 2014

Developed by: Amarin Corp.

Rights: Marketed by Amarin

Capsules contain an ethyl ester of at least 96 percent EPA

The global EPA and DHA finished product market has a projected annual growth rate of 6.1% for 2020-2021.

—GOED 2020 Global EPA & DHA Finished Products Report

Pharma will most likely have to look beyond its established sources of APIs in order to obtain omega-3s.

"You typically don't see a traditional pharma API manufacturer getting into the omega-3 space very often, largely because the technology required is fairly specialized," says Ismail.

KD Pharma, the largest manufacturer of omega-3 APIs for pharma in the world, has a deep portfolio that includes multiple state-of-the-art purification technologies, which allow for the production of high-quality, pure omega-3s with EPA concentrations as high as 99 percent.

While pharma's participation in the omega-3 ingredient market will likely not cause a supply shortage, the demand for high EPA oils may shift the price of ingredients for other industries.

"I think that the oils that exist that are high in EPA are going to increasingly end up in the pharma market," says Bernasconi. If the supply of these oils starts dwindling and ingredient manufacturers have to reach into other oils, it could change the price of the ingredients.

"This might also increase the price of high EPA oils for the dietary supplements industry, and potentially lead to changes in dietary supplement formulations," says Bernasconi.

CATCHING THE BIG FISH

While the U.S. did not see its first omega-3 drug approval until 2004, prescription EPA has been marketed in Japan for over three decades. In 1990, Epadel, developed and marketed by Mochida Pharmaceutical and EPA supplier Nippon Suisan Kaisha, became the first prescription drug in the world to successfully extract high purity EPA from omega-3 fatty acid.

The drug is credited for opening a new field in the treatment for arteriosclerosis obliterans and hyperlipidemia (cardiovascular conditions) and was the leading drug in its class in Japan for 20 years. Epadel reached

Omega-3 drug hopefuls

CaPre

Krill-oil derived combination of EPA and DHA

Company: Acasti Pharma | Québec, Canada

Target indication: Severe hypertriglyceridemia

Status: Acasti submitted its briefing package, which included results from a double-blind, placebo-controlled, 26-week, two-trial phase 3 clinical program, to the FDA on April 29, 2020. Acasti is currently awaiting comments, and expects a formal response from the FDA by June 30, 2020.

Edasalonexent

Small molecule drug containing a combination of salicylic acid and DHA

Company: Catabasis Pharmaceuticals | Boston, MA

Target indication: Duchenne muscular dystrophy

Status: Currently being studied in a one-year, randomized, double-blind, placebo-controlled phase 3 trial, as well as in an open-label extension study. Top-line results from the phase 3 trial are expected in late 2020 and the trial is anticipated to support an NDA filing in 2021. Catabasis is also planning a clinical trial to study edasalonexent in the non-ambulatory Duchenne population.

Alfa

Highly purified EPA in gastro-resistant capsule

Company: KD Pharma, SLA Pharma | Bioggio, Switzerland; Liestal, Switzerland

Target indication: Familial adenomatous polyposis; secondary indications for ulcerative colitis and sporadic polyps

Status: Successfully completed phase 1 and phase 2 studies and in the process of conducting phase 3 trials in the EU for the orphan drug indicated for the treatment of FAP. A phase 2 trial testing Alfa in ulcerative colitis and preclinical testing in sporadic polyps is underway. The drug, under the name EPAspire, is also entering trials to mitigate the severity of COVID-19.

MAT9001

Highly potent combination that includes a sizable dose of EPA, low amounts of DHA and the addition of DPA, delivered via gelatin capsule

Company: Matinas Biopharma | Bedminster, NJ

Target indication: Severe hypertriglyceridemia

Status: Currently in phase 2 clinical development, with one completed study evaluating the drug's bioavailability and potency against Vascepa. In March, the company initiated a pharmacodynamic study of MAT9001 against Vascepa in patients with elevated triglycerides. Topline results expected late 2020. Pending discussions with the FDA, the

In the $1.4B omega-3 ingredients market, 2% of volume, which equates to 13% of value, is attributed to the pharma industry.

—GOED 2018 Global EPA & DHA Ingredient Report

peak sales of $481 million in 2012, after which it faced government price cuts and generic competition.

In June 2018, Mochida announced a partnership with Amarin focused on the development and commercialization of EPA-based drug products in the U.S. and certain other territories.

The biggest fish in the U.S. sea is currently still the first out of the gate. Lovaza, a drug developed by Norway's Pronova BioPharma, was launched in the U.S. as well as in major European markets (under the brand name Omacor) in 2005. In 2008, as the drug's global sales reached $778 million, GlaxoSmithKline spent $1.65 billion to buy Reliant Pharmaceuticals, the company that was licensing the rights to Lovaza in the U.S. and Puerto Rico. Lovaza rose to blockbuster status in 2010, maintaining annual sales of approximately $1.1 billion until facing generic competition in 2014.

Investors had high hopes for Vascepa, the sole product from Dublin-based Amarin. Last year, analysts anticipating the FDA's favorable decision on Vascepa's label expansion were abuzz about a potential buyout of the small biopharma company. Big names in pharma were added to the possible suitor list, all chasing Amarin's potentially game-changing omega-3 treatment.

This scenario, of course, is not unusual in pharma.

"Over the last few years, Big Pharma has shown high interest in smaller niche companies with novel promising therapies," says Arda Ural, PhD, the Americas Industry Markets Leader for Health Sciences and Wellness at EY. "For example, smaller companies with their omega-3 products can be potential targets for Big Pharma companies for M&A deals and partnership/collaboration agreements."

After a huge first-quarter revenue bump, Amarin hit a snag this April, losing a patent trial against two generic drugmakers. This ruling subsequently cleared the way for Hikma Pharma's approval for a generic

version of Vascepa in late May. Amarin has appealed the court decision, so it remains to be seen if any generic company takes the risk of launching a generic version during the patent litigation appeal process.

Despite some uncertainly, market experts at Evaluate Pharma estimate that worldwide sales of omega-3 drugs will reach close to $1.4 billion in 2021 — a 40-50 percent increase over 2019.

SEA OF POTENTIAL

The year kicked off with news from two promising late-stage omega-3 trials — unfortunately both outcomes were less than ideal.

AstraZeneca, which had acquired Epanova along with developer Omthera Pharmaceuticals in 2013 in a $443-million deal, made the decision in January to shutter a trial after disappointing preliminary data.

Hoping to reach a broader patient population, the drugmaker had launched a large, five-year phase 3 outcomes trial shortly after Epanova won FDA approval in 2014 for patients with severe hypertriglyceridemia. But then preliminary data showed Epanova had a low likelihood of benefiting patients with an increased risk of cardiovascular disease, so AstraZeneca pulled the plug.

The second trial fail came from Canadian drugmaker Acasti Pharma. In January, Acasti announced that the phase 3 trial testing its drug hopeful CaPre, a krill-oil derived combination of EPA and DHA for the treatment of severe hypertriglyceridemia, had missed its primary endpoint.

But all may not be lost for CaPre. The company believes that EPA and DHA are more efficiently transported by phospholipids sourced from krill oil than the EPA and DHA contained in fish oil transported by ethyl esters in other prescription omega-3 drugs. Undeterred by the trial results that Acasti attributed to a highly unusual placebo effect, the company submitted a briefing package to the FDA for review, and are now awaiting a formal response on CaPre.

But current trials are not limited to the cardiovascular space.

Boston-based Catabasis is studying a small molecule drug that contains two active substances, salicylic acid and DHA, as a potential novel treatment for Duchenne muscular dystrophy (DMD). The FDA has granted the drug, called Edasalonexent, Orphan Drug, Fast Track and Rare Pediatric Disease designations for the treatment of DMD. Results from the phase 3 study are expected by the end of this year, and Catabasis hopes to file its New Drug Application (NDA) in 2021.

KD Biopharma and SLA Pharma's highly purified EPA formulation, called Alfa, is in a

phase 3 trial in the EU for the treatment of familial adenomatous polyposis (FAP). Currently, there are not safe treatments for FAP and a partial or full removal of the colon is considered the "gold standard" of care. Alfa has been granted Orphan Drug designation in the EU and U.S. Early stage trials are also testing Alfa in patients with ulcerative colitis and sporadic polyps.

The varied and wide exploration of omega-3 treatments is not surprising, according to Bernasconi.

"Omega-3s have, among other biological functions, anti-inflammatory properties and inflammation is in some way connected to most common chronic diseases," he says.

Omega-3 fatty acids can reduce the production of molecules and substances linked to inflammation, such as inflammatory cytokines. It's for this reason that numerous omega-3 drugs are being explored as possible COVID-19 treatments.

Data from the late-stage KD Pharma/ SLA Pharma FAP trial suggests the drug candidate could suppress the expression of inflammatory cytokines believed to contribute to the progression of more serious COVID-19 symptoms. The Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK has already given the trial a green light.

A Canadian non-profit physician organization, the Canadian Medical and Surgical Knowledge Translation Research Group, is sponsoring a trial to test the potential anti-inflammatory effects on lung tissue as well as the potential antiviral/ antimicrobial effects that Amarin's Vascepa could offer COVID-19 patients. Again, the goal is mitigating severity in COVID-19 infection.

BEYOND THE SEAS

In the U.S., commercialized omega-3 drugs are still part of an exclusive club — but all signs point to an expanding membership.

There are large markets for omega-3 products around the world — so products approved in the U.S. have opportunity beyond FDA borders.

Evaluate Pharma estimates that worldwide sales of omega-3 drugs will reach close to $1.4 billion in 2021 — a 40-50 percent increase over 2019.

"Approval in China, for example, will have a big impact on demand for omega-3 pharmaceuticals," says Ismail.

There are currently no prescription omega-3 products in China. The country's large population and high prevalence rates of hypertriglyceridemia suggest that China could greatly benefit from the introduction of omega-3 pharmaceuticals. Amarin recognized this need in 2015, forming a $169 million partnership with Eddingpharm to develop and commercialize Vascepa in China; trials are currently underway.

Researchers are also exploring other omega-3s, such as DPA (docosapentaenoic acid) and ETA (eicosatetraenoic acid), as well as fatty acids beyond the omega-3 space.

"Omega-3 pharmaceuticals have triggered new research in a lot of other fatty acid areas," says Ismail.

For example, omega-6 fatty acids, which typically come from vegetable oils and seeds, appear to help keep good and bad cholesterol in a favorable balance.

"There is certainly more to come," says Ismail. "Not only is there growing interest in the space, the landscape is constantly changing."

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An easier pill to swallow

A robust OSD development strategy will bring complex products to market faster and more efficiently

By Kieran Coffey and Sandra Conway, Technical Services Leads, Pfizer CentreOne

Oral solid dose (OSD) continues to be the dominant drug delivery form, used for a wide range of treatments and accounting for more than 50 percent of novel drug approvals in 2019.**1** Within the development of OSD formulations, a broad range of coating technology platforms have brought many benefits to drug products, such as improved stability, integrity and robustness, while improving delivery and making them more resilient against environmental changes.

Today, the increasing complexity of molecules in the drug pipeline is bringing greater challenges in formulation and scale-up. OSD manufacturers must be armed with a breadth of technology and expertise from a multidisciplinary team. Here are a few strategies and coating technologies that can aid complex OSD formulation.

LAYING THE FOUNDATIONS

Understanding and experience form a basis for any OSD development project. This depth of understanding ensures process robustness, regulatory assessment and process optimization are built in from the beginning. Each project should begin with risk assessment that captures the potential risks and challenges. This forms the first element of your development plan.

A common pitfall at this stage is that technical considerations for scale-up and the impact of materials from an active

pharmaceutical ingredient (API) and excipient characterization perspective are not obvious or an area of focus. This includes the interactions of API and excipients as well as any environmental and processing conditions that may impact the API such as humidity or temperature. The formulation may also impact the choice of equipment design, which could come into play if, for example, the process requires solvent rather than aqueous coating.

Equipment design should be considered early in the development cycle with an eye on the full-scale capabilities available. The small-scale work should replicate the intended process train as closely as possible, so that the learnings made at small scale can inform the full-scale equipment design and be readily scalable.

The time investment on understanding the API and excipients and the interactions at a small scale will be paid back several times over further down the line. This understanding of the API and excipient chemistry also creates the basis for a robust cleaning process.

The understanding of the process and its design space is now an expectation of regulatory bodies for any new or transferred process. Data from small scale manufacturing during development work is a key part of that knowledge-gathering activity. With well-designed and scientifically justified trial work, efficiencies in time and costs can be made through reduction of work required at full scale. This should take the form of the well-established Quality by Design framework as per the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q8 guidance. Most importantly, this approach will allow for a more robust and reliable full-scale process. In practice this will require that companies design experiment-type trials at a small scale that will define the design space for the scaled-up process.

THE STEPS TO COATING SUCCESS

Coating unit operations are a good example of how to develop a robust process during scale-up or tech transfer. In pharmaceutical oral solid dose manufacturing, coating is often a final cosmetic step that is not seen

IMAGE COURTESY OF PFIZER CENTREONE

Equipment design should be considered early in the development cycle with an eye on the full-scale capabilities available.

as critical. However, coatings can be essential components, particularly for modified release or combination products. Coating also involves a wide range of different technologies from sugar to film, pans to fluid beds, and tablets to multiparticulates.

Whatever the application, the approach should remain the same. The process inputs should be detailed and characterized. Wherever possible, any variation should be removed and where this is not possible, the inputs should be controlled. If this can be successfully achieved, it will allow the process to be modeled. This means that that we can mathematically replicate how the process will behave and predict the output. This will aid scale-up and transfer and can also lead to greater control of the process.

Modeling of the process removes much of the risk associated with a scale-up or transfer project. As previously highlighted, this includes a robust understanding of the API and excipients, however all inputs should be considered, including all the materials from upstream in the manufacturing train. The cores or multiparticulates should have a known and controlled size and weight, and the coating material attributes should have set specifications particularly around particle size, density and viscosity. Small scale trials will also allow the design space to be built for these material attributes.

For coating operations, the spray zone, mixing and thermodynamic balance are of great importance to process understanding and robustness. A coating operation is a balance of the mass and energy going into and leaving the pan. If all inputs can be measured and controlled, and all activities taking place in the pan can be characterized, the outputs (e.g. conditions of the exhaust air) can be predicted. In a coating operation, the model should allow for the heat and volume of the input air and suspensions and ideally allow for any heat loss from the system. The use of solvent versus aqueous coating will also impact the calculations and should be accounted for in the model.

Through understanding and control of the inputs and by removing variables where possible, thermodynamic models have been created that greatly enhance the success rate of scaling and transfer operations. Building a model that predicts exhaust

stream conditions can ensure that the conditions that tablets are encountering in the pan are thermodynamically the same regardless of the scale of the pan.

Another technique that is very useful is coating by trend. In a controlled environment there will always be some fluctuation in point data. As it is a dynamic environment, the individual parameters will move and compensate depending on the tuning of the control loops and natural fluctuation. Therefore, watching the real-time trend of the data generated rather than monitoring data points is more useful. Inflection points should be looked for in trend lines that start to diverge or converge because this means that the balance in the coating pan has changed. Once again, this is a scale-independent way to ensure that a process is behaving in a similar manner across equipment. This should all align with the model that was developed during small scale trial work.

Today the industry trend is toward continuous processes and there are many solutions from equipment vendors to help achieve that goal. Film coating can be truly continuous, but most coating processes use a plug flow type process, which also works well for modified release or combination products. Whether it is continuous, plug flow or batch, the principles remain the same: Understand the inputs, remove variation where possible and control the controllable. The goal for anyone working in this area is to be able to predict how these principles are achieved.

BEYOND THE MACHINE

Successful coating projects call for expertise and capabilities that go beyond technology and machinery. A successful cross-functional team should always include development scientists and engineers. This should also include the expertise from operations, analytical, statistics and regulatory team members. However, with the current expectation on the level of process controls, it should also include the Process Analytical Technology (PAT) team. A high level of data analytics from equipment connectivity and PAT is needed to ensure real-time monitoring during manufacturing through to product testing and release.

PAT should be integrated at various points to help build a robust process and feedback control, where required. This can then

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translate into using multivariate models to integrate "coating by trend" into the control strategy for the product; even to allow end-point determination using soft sensors or a PAT/soft sensor hybrid approach.

To have the right experience in place, the skill set of a project team should ideally cover data analytics, equipment design, manufacturability, process robustness, physical characterization, and quality systems. Fostering collaboration between the various disciplines involved is also vital for success and is driven through a robust project plan lead by a project lead. By having members from different disciplines actively participate in every aspect of the project, team members can build an understanding outside of the confines of their own responsibilities and understand the work, challenges, issues and results at every development step. This collaborative environment means that decisions can be made based on the needs of an end-to-end project as opposed to a single stage. An engaged team from the process floor up can identify potential issues and proactively solve them. The goal is to limit process issues that could impact a timely delivery.

In the above example, a high-level view of the development of coating operations was described, but the principles apply across all unit operations. Coating is one of the more complex processes to model and characterize due to the number of inputs and variables. However, by demonstrating success with coating operations a roadmap for every process is easily seen.

FINAL THOUGHTS

Successful OSD projects demand strong foundations to be laid during the initial stages. Understanding all the inputs from material attributes to product release, having the right equipment design, process monitoring, quality systems and working with an inter-disciplinary team are all crucial to ensuring that projects meet their goals.

By appreciating the requirements of each of these areas, the development process can be optimized. A clear line of sight from initial development work through to the final scaled-up commercial process should be evident with all risks identified from initial assessments mitigated prior to validation. The product lifecycle from design to validation through to continued process verification requires a robust development strategy. As development strategies become increasingly complex, there is also much value to be gained though collaboration and interdisciplinary teams. This approach can result in bringing quality products to market faster and more efficiently; irrespective of how complex the formulation or process.

REFERENCES

1. *FDA, New Drug Therapy Approvals 2019. fda.gov.*