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Karen Langhauser
Chief Content Director

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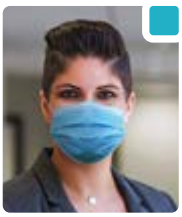
Fish oil salesmen

Pharma explores the promise and realities of prescription omega-3s



The critiques of fish oil — the commonly use term for omega-3 fatty acids — are varied, creative and harsh. The family of critical polyunsaturated fats have been called everything from "fish tales" to "fool's gold" to "foes." And those peddling the benefits of omega-3s haven't fared much better, being dubbed "snake oil salesmen" on more than one occasion.

Ironically, that last claim is somewhat accurate.

Starting in the mid-1800s, thousands of Chinese workers came to the U.S. as indentured laborers to work on the Transcontinental Railroad. They brought various Chinese medicines with them, one of which was snake oil. After a hard day's work laying tracks and driving spikes into mountains by hand, the workers would rub oil made from the Chinese water snake on their joints.

The oil was quite effective in reducing inflammation. So effective that some enterprising Americans decided to make their own and hawk it as a cure-all. (As it turns out, the dry, 19th century frontier lacked a supply of Chinese water snakes and mineral oil was a poor substitution, which eventually gave "snake oil" the bad rap it carries to this day.)

Over a century later, an analysis published in the Western Journal of Medicine revealed why the Chinese water-snake oil was so effective — it contains 20 percent eicosapentaenoic acid (EPA) — the same critical omega-3 found in fish oil.

To date, there are more than 42,000 published studies, including 4,000 human clinical trials, on EPA and its important counterpart, docosahexaenoic acid (DHA). In many ways, the abundance of information and interpretation of data has created more confusion than clarity.

But still, this vast body of research overwhelmingly supports the health benefits of omega-3s in areas such as cardiovascular health, mental health and depression, gastrointestinal diseases, eye diseases and even rare genetic disorders. Benefits like these have caught the eye of the pharma industry.

True, omega-3 pharma applications have been somewhat limited. There are just four branded drugs approved by the FDA with omega-3 fatty acids as active ingredients, and only two of those drugs are commercially available in the U.S. Until recently, all of the approvals were restricted to the same niche patient population – adults with severely high triglyceride levels.

And yet, one of those drugs (GSK's Lovaza) reached blockbuster status in 2010 and the second (Amarin's Vascepa) is close behind. In late 2019, Vascepa's approval was expanded, making it the first and only drug approved to reduce cardiovascular risk among patients with elevated triglyceride levels — and greatly widening the treatment population.

In addition to approved drugs, there are currently 88 drugs in pharma's preclinical and clinical pipeline that use EPA, DHA or derivatives — some of which are seeing promising results in late-stage trials.

As the clinical and financial significance of omega-3 treatments continues to grow, pharma might just become the newest version of snake oil salesmen — but this time around, the elixir works.

industry dose

Binge worthy: Virtual events on demand

Check out what equipment suppliers have to offer, from the safety of your desk

When it comes to new equipment and technology geared towards pharma manufacturing, many vendors rely on industry tradeshows and events to unveil their offerings. With most major in-person events being postponed or canceled, the industry has lost its traditional platforms for sharing innovation.

But pharma equipment suppliers rarely disappoint with new technologies and capabilities, and now they are bringing that same level of innovation to digital platforms.

While you may not be able to shake hands and drink overpriced trade event coffee, pharmaceutical manufacturers can still experience the newest technology innovations, glean industry insights and make important connections.

Pharma Manufacturing has started an ongoing list of virtual experiences — from press conferences to trade show booths. Visit our website to peruse the links and tour current on-demand offerings from some of our favorite equipment suppliers.

Here is a snapshot of a few recent virtual events, all available to view on-demand:

Virtual Showroom | Romaco

In early May, Romaco premiered its newest products in a digital space. Visitors can take a virtual tour through a spacious showroom where the supplier of all-in-one solutions has various technologies on display for manufacturing, tableting and packing solid dose pharmaceuticals.

The Romaco virtual showroom is a great opportunity to browse, with plenty of interactive elements that make technologies more tangible.

Read more about pharma's dive into the omega-3 seas on page 10.

Market experts estimate that worldwide sales of omega-3 drugs will reach close to $1.4 billion in 2021 – 40-50% growth from 2019.

Next to each machine are various links to more information. Short videos take the place of face-to-face communication. Visitors can use the online chat feature to ask questions.

Product Inspection Virtual Trade Show | Mettler Toledo

Visitors to Mettler Toledo's platform are guided through the company's extensive range of product inspection solutions. Keynote presentations around food/pharma safety and smart factory solutions are available, as well as detailed discussions about smart factory connectivity.

Virtual Pharma Expo | Pharmaceutical Online/ Techceuticals

Fellow trade pub *Pharmaceutical Online*, in collaboration with Techceuticals, launched an inaugural Virtual Pharma Expo Conference on May 20. The free event features 15-minute presentations by leading experts from 12 major pharma solid dose equipment manufacturers including Glatt, Natoli, Fette, Syntegon, KORSCH and ACG.

Virtual Online Booth | Dorner Conveyors

Dorner's virtual booth showcases the exciting products the company was planning to display at Interpack this year: a combination of conveyors and chutes, that together create a flexible package product line. Visitors can learn about new products, watch the trade show video, and chat with experts.

vLC-MS Virtual Event | Thermo Fisher Scientific

Thermo Fisher's virtual event offers a series of presentations and exhibits. The company showcases its newest instruments, software and workflow solutions. Digital programs will enable scientists to broaden mass spectrometry-based research, from proteomics and biotherapeutics to clinical applications.

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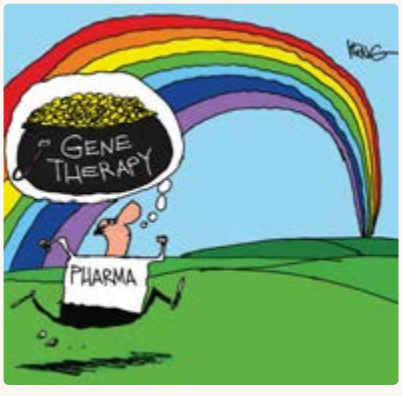

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— **John O'Neill**

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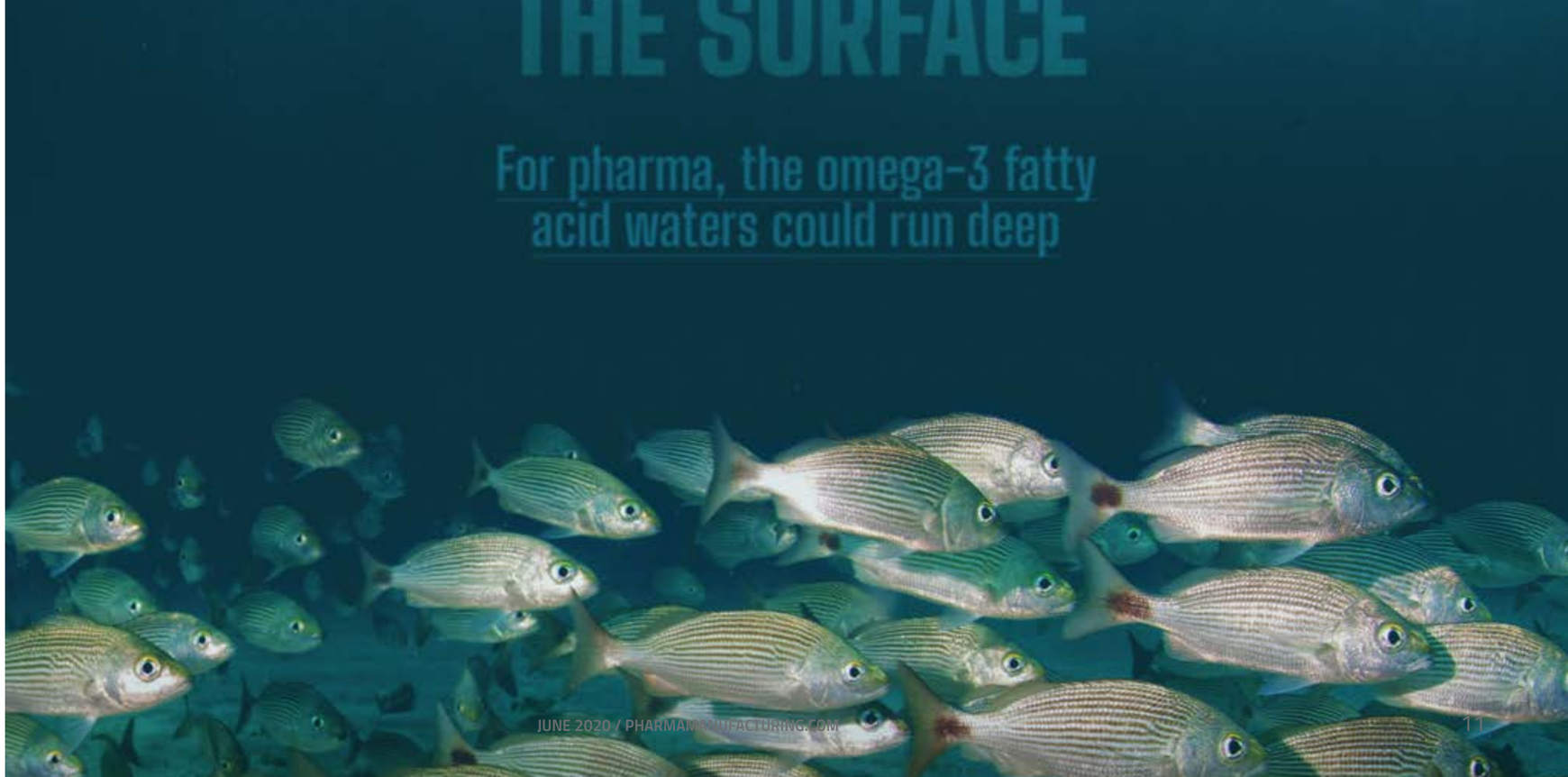
Karen Langhauser
Chief Content Director

BEYOND THE SURFACE

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



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 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.

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 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

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

— GOED 2020 Global EPA & DHA Finished Products Report

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

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, GlaxoSmith-Kline 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

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 company plans to conduct a placebo-controlled phase 3 study assessing the efficacy of MAT9001 in patients with severe hypertriglyceridemia.

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.

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

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.

"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."

Meagan Parrish
Senior Editor

Focus on: Russia

After building its domestic infrastructure, Russia's pharma industry looks to go global

It was hardly a blip in the news last month when the director of one of Russia's leading research institutes said they could be ready to start a mass vaccination campaign against the coronavirus by fall. Plenty of other pharma companies in the hunt for a Sars-CoV-2 vaccine have stolen headlines around the world in recent months, but the work of Russian scientists combatting the pandemic has largely remained in the shadows. Now, it's possible that's about to change.

While the eye-popping claim that a new coronavirus vaccine could be ready for roll-out within a few months was clearly ambitious (and most likely overly optimistic), the efforts illustrate a rising aim in Russia to make a bigger mark on the global pharma scene.

Although Russia has long been a leader in other scientific fields, its pharma segment has failed to become a hotbed of technological advancements. Instead, the industry has been dominated by state-controlled policies, a high rate of imports and low-cost generic manufacturing. However, Russian leaders are now on a quest to bolster R&D investments in pharma and put the industry on track to increased independence and innovation. To achieve these goals, the industry will have to clear several major hurdles.

Government involvement

On the surface, Russian pharma patients have been given a sweet deal. Under the country's state-controlled health care system, Russian citizens have been guaranteed access to all inpatient drugs as well as many outpatient drugs for free. Naturally, the government wants to procure these essential medicines on the cheap, however this has created other challenges in the market.

For example, price caps determined by the government for essential drugs have made it difficult for local manufacturers to make money on drug production, despite prices being set to allow for 30 percent in profit (maximum). The emphasis on getting low-cost drugs has also contributed to the country's reliance on generic medicines. And because there are not enough local producers of APIs on the domestic market, the industry is also heavily reliant on API imports for manufacturing from China and India.

So, in 2011, the Russian government launched an initiative called Pharma 2020 to lay the groundwork for more domestic pharma production. At the time, about 90 percent of the drugs on Russia's market were imported and the goal was to reduce that figure to 50 percent. Nearly 10 years later, Russia is headed in the right direction but is still importing about 70 percent of its drugs.

Meanwhile, growth in Russia's pharma market appears to be increasing each year, but only modestly, and the growth has been slowing. According to Oleg Berezin, a partner and the head of the Life Sciences and Healthcare group at Deloitte, the country's pharma industry grew by 9.5 percent (in Russian ruble terms) in 2019, but after adjusting for inflation for drugs, the real growth was only about 7 percent. This year, the market is set to grow more, but mostly due to inflation and government spending.

"We don't have double digit growth like we had five years ago," Berezin says. "Currently the market is not just stagnating — there is small growth."

Still, the Russia government's use of financial instruments such as tax benefits and subsidies has helped breathed some new life into the pharma market. In 2018 alone, 12 new large production sites were opened in Russia.

The cash flow has also helped buoy scientific progress in drug development. In the last few years, Russian pharma companies have introduced several new drugs onto the market including a next-generation protease inhibitor for hepatitis C developed by R-Pharm, and the world's first approved biosimilar for dornase alfa, a cystic fibrosis treatment, made by Moscow-based Generium.

Yet, low drug prices are continuing to create roadblocks for local drugmakers. In April, a group of seven manufacturers informed Russia's Industry and Trade Ministry that they may have to stop making about 50 essential medicines because the cost of production now exceeds the sale price, partly due to the devaluation of the ruble and rising API prices caused by COVID-19.

The next move

Now that more infrastructure has been built to produce pharmaceuticals, the Russian government is looking to take the next step and invest in long-term industry growth and globalization. Today, a new initiative called Pharma 2030 is in the works, which Berezin says will attempt to make the country's pharma industry more competitive and innovative.

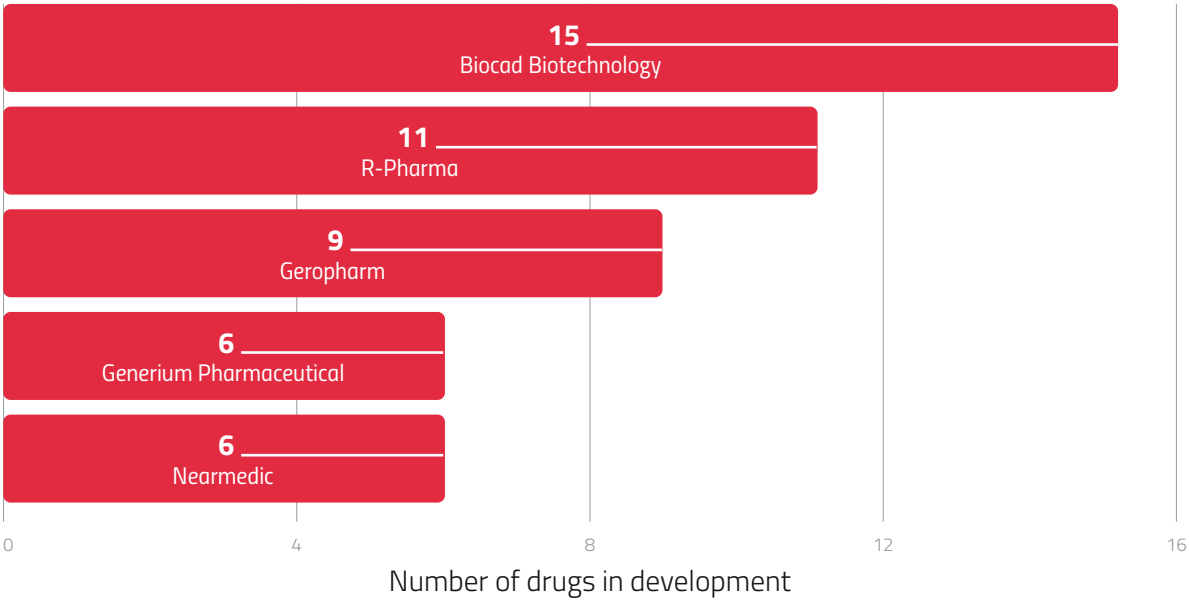
Berezin says that Russia has enough facilities for finished dosages to make most essential drugs onshore, so the focus is now on decreasing imports of APIs.

"We already have some incentives for local producers of APIs," he says. "There are specific benefits and incentives with respect to drugs that are sold to the government and produced locally, which are even larger if a drug is produced out of local APIs."

The bigger challenge, Berezin says, is going to be boosting the development of first-generation therapies and transforming the industry into a high-performing export-oriented sector, which is another goal of Pharma 2030.

"There is not enough financing for R&D from Russian pharma

Russian pharma companies with the biggest pipelines



INFORMA PHARMA INTELLIGENCE

companies or Big Pharma companies, which generally don't have R&D activity here except for clinical trials," he says.

One mechanism that could be created by Pharma 2030 is the support of more joint ventures for pharma companies looking to enter emerging markets. A specialized venture fund could also further support pharma innovations.

The trick will be balancing Russia's historic isolationism and emphasis on the domestic production of low-cost drugs with the desire to be competitive on a global level.

It's also unclear to what extent the initiative will make Russia an attractive destination for investments from multinational pharma firms. Although several Big Pharma companies — such as Novartis, AstraZeneca and Sanofi — operate in Russia, the current emphasis is on producing drugs for the local market in a wide range of therapeutic areas such as oncology, diabetes and cardiology. However, Berezin says that some, especially those that do not have local manufacturing facilities, lose market share due to the preferential treatment given by Russian government contracts to local manufacturers.

The digital landscape

Modernizing the country's pharma sector is top-of-mind for Russia's industry. To that end, Russia has mandated new track and trace regulations that are currently scheduled to go into effect on July 1 (although the deadline could be postponed). Similar to other programs around the world, Russian pharma manufacturers will have to report every step their products take through the supply chain, as well as pricing information. Ultimately, the goal is to reduce the presence of any counterfeit drugs or other illegal practices on the market.

And Berezin says that if producers and market authorization holders have all of their drug data reported by the entire supply chain to the system, it will create a big opportunity to use and analyze this data.

In general, however, the pharma industry in Russia has been slow to adopt digital tools. Only about one-third of Russian companies who responded to a recent survey conducted by Deloitte said they

have implemented a digital strategy. Although companies understand that there are advanced solutions available, many still rely on websites and social media as their only digital tools.

"In this particular area, the Russian market has a long way to go, but recent regulatory developments, such as a green light for OTC online sales, will likely boost it," Berezin says.

The COVID-19 effect

The effort to be the first country that successfully secures a coronavirus vaccine has echoes of the old space race. Will Russia pull off another Sputnik?

Russia's deputy prime minister for Social Policy, Labor, Health and Pension Provision, Tatyana Golikova, has stated that the country has 47 coronavirus vaccines in development, although just 10 have been recognized by the World Health Organization. Clinical trials on at least two candidates are set to begin this month, and the hope is that at least one candidate could be registered with local regulators by fall.

The country has plenty of reasons to want to rush progress. To date, Russia has the third highest number of coronavirus cases in the world, and securing a vaccine will be a crucial step for the country's recovery.

Russia is also working on new treatments for the coronavirus, and the CEO of the Russian Direct Investment Fund made a bold claim in May that its scientists have developed "perhaps the most promising COVID-19 drug in the world." The drug, called Avifavir, is based on an existing flu treatment that Russian researchers have enhanced. Early results from a study of 330 participants showed that it can reduce the duration of the coronavirus to just four days in some patients.

Developing a game-changing treatment or being the first country to approve a coronavirus vaccine would make a definitive statement about the capabilities of Russia's pharma industry. As the country moves to bolster its ability to be an innovative force in pharma, its efforts to fight the coronavirus could help put Russian drugmakers on the global pharma map.

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Making the change with cleanroom air

Analysis shows how a facility can benefit from lower air change rates without risking non-compliance

Regulatory bodies around the world require that cleanrooms meet the allowable particle counts as required per their classification. Most pharmaceutical manufacturers take a conservative approach to ensure compliance with particle count limits and often, this is based on historical data from previous projects where air change rates are set at a very high level, relative to the need.

There are many factors that contribute to varying particle counts to fluctuate between facilities, including process functions, air filtration equipment, physical design, human activity and level of gowning, surface deposition, cleaning regiment and frequency and space pressurization.

Test data for an ISO 8 cleanroom with 20 air change per hour (ACH) found that particle counts were typically below 1,000 parts per million (ppm) and peaked at 2,241 ppm, a level that is considerably below the required particle count of 100,000 ppm. Similar observations were made for ISO 7 rooms with 40 air changes per hour. Particle counts were below 1,000 ppm with an allowable particle count of 10,000 ppm.[1] This data entices us to look deeper into the design for air changes.

Reduction of air change rates in cleanroom applications is desirable to reduce energy consumption. However, there are concerns that there is not an easy solution if particle counts are above the acceptable level. How can a facility benefit from lower air change rates without risking non-compliance — and what is the level of energy and cost savings that can be expected?

Basis for analysis

The authors reviewed two scenarios:

1. The size of an air handler for design flow rate with a 10 percent safety factor on airflow, with static pressure accounted for. This will be reviewed for design air change rates between 10 and 45 for various climate and utility base cost locations.
2. The energy consumption impact of operating between 10 and 20 ACH on a system designed for 22 ACH (20 ACH plus a 10 percent design margin).

The analysis is focused on air change rates. All of the other aspects of the design remained the same, including space temperature and humidity; volume; internal heat loading; no exterior walls and fixed outdoor air volume to account for pressurization leakage and code compliance.

The cleanroom: The suite is based on a volume of 81,330 cubic feet (cu ft), with air change rates from 10 to 45 ACH. The main suite is 77,692 cu ft, and the remainder is split between four airlocks. The airlocks are supplied with five ACH greater than the process room to allow for clean-up. Internal lighting/process loading assumed at 3.07 British Thermal Unit/square foot (Btuh/sf), and 6.82 Btuh/sf respectively.

Utility generation and costs: The base analysis assumes heating hot water is generated with a natural gas steam boiler with a steam-to-hot water converter at 82 percent efficiency. This includes distribution losses and on design cooling day with adjustments made for variations in combustion air temperature throughout the year.

Using steam for a heating source is typical for GMP pharmaceutical facilities. Chilled water generation for cooling was based on a chiller plant with cooling towers. Utility and air-side equipment is compliant with ASHRAE 90.1.[2] Trane Trace 700[3] was utilized for annual energy models on an hourly basis over an entire year for each site.

FIGURE 1

Annual utility cost

ACH	Chicago	Newark*	Raleigh	San Francisco
45	$104,344	$173,566	$101,413	$210,240
40	$93,149	$155,015	$90,653	$187,590
35	$81,951	$136,452	$79,862	$165,022
30	$70,660	$117,820	$68,893	$142,232
25	$59,375	$99,002	$57,909	$119,205
20	$48,050	$80,188	$46,841	$96,291
15	$36,657	$61,253	$35,831	$73,177
10	$25,227	$42,176	$24,431	$50,064

*Newark and San Francisco costs are significantly higher due to higher utility rates. Refer to Figure 2 for energy consumption by city and air change rate.

Site selection: The analysis includes air change rates between 10 and 45 ACH. Four different locations were reviewed: San Francisco, Chicago, Raleigh, and Newark, New Jersey.

These sites were selected for a wide range of climatic conditions. Climate modeling data came from the National Oceanic and Atmospheric Administration. Data included average hourly data for an entire year. Utility rates were based on industrial utility rates for each location.

The findings for the analysis are shown in Figures 1 and 2.

Findings across sites

San Francisco has the lowest energy consumption, but the highest utility cost due to utility rates. Figure 2 presents a linear relationship between airflow rate and energy consumption. If a pharmaceutical manufacturer chooses to run at 20 ACH when 10 ACH is sufficient, the additional utility cost increase per year is significant, at between 84.8 and 96.7 per cent, depending on location. Typically, HVAC utility costs account for roughly 60 percent of a GMP pharmaceutical facility's total utility cost.[4]

Our analysis across these locations shows that while utility rates vary by location and have an impact on facilities' energy costs, differences in ACH levels play an even more significant role and can lead to significant savings in annual costs. As HVAC utility costs account for more than half of a pharmaceutical

facility's total utility cost, careful consideration needs to be given to operating ACH rates and cost impact. Considering the potential energy savings for a single system, the site-wide energy savings when multiplied over the number of cleanroom HVAC systems that may be able to run at a lower air change rate is significant. The potential to reduce overall site utility cost is substantial.

However, designing an air handling system with the sole purpose of meeting particle limits has significant risk if the required air change rate is underestimated.

Analysis of HVAC system size

The same clean space model was used as a basis for this analysis. Raleigh was used as the sample location. The energy cost at airflows between 20 and 10 ACH was compared for two different systems:

1. Air handling unit with one supply fan and one return fan designed at 22 air changes per hour (20 ACH plus 10 percent margin).
2. Air handling unit sized to meet the air changes per hour with a 10 percent design margin. Pressure drops were adjusted as the square of the flow for most component, filter losses were provided by filter vendor at the varying airflows.

It was assumed that pressure drop through the venturi-valves did not change. Total system pressure reduces as the operating airflow rates are reduced, and the system becomes more oversized. Motors/variable frequency drives (VFDs) experience reduced efficiency as the load becomes smaller. As VFD/motor efficiency decreases, the system pressure drop savings offsets this inefficiency.

As the air change rate reduced from 20 to 14 ACH, the systems sized for 22 ACH shows an increasing savings over the system sized for the load due to reduced pressure drops in the system. As the system airflow drops below 14 ACH, the fan motor and VFD losses start to become significant offsetting the reduced fan load based on reduced airflows and pressure drops. Either way, the system designed for 22 ACH provides better performance at lower airflows down to 10 ACH.

Considering a fan array option, some fans can be shut down as the airflow drops, allowing the fan and VFD efficiency to be maintained, resulting in higher energy savings at the lower air change rates versus the system with a single supply and return fan.

However, this comes at the cost of lower efficiency at design conditions due to the smaller wheel diameter of the fans in the array and the generally decreasing efficiency with decreasing wheel diameter.

The fan power cost as a portion of overall utility cost for the cleanroom air handling system is significant, varying between 53 and 68 percent of the total system utility cost, depending on the various options reviewed. This being the case, the biggest savings at the lower air change rates is fan power.

Figure 3 provides utility cost broken down by utility with fan power separated out of HVAC utility electrical costs such as chillers, pumps, tower and boiler fans. By far the largest portion of savings is in the reduction of fan power. This demonstrates that sizing the air handling system for what is believed to be the worst case and commissioning the system to a lower airflow has merit.

Based on the data, sizing an HVAC system to ensure the air change rates at design will meet the cleanroom classification requirements and then working to reduce airflow at plant start-up would be a reasonable approach. The question becomes: Are there potential issues with a system running at a lower airflow rate than designed and are there any code issues that may be a hinderance?

Portions of the system may need to be revisited from an oversizing

FIGURE 2

HVAC energy density vs. air changes/ hour system designed for airflow

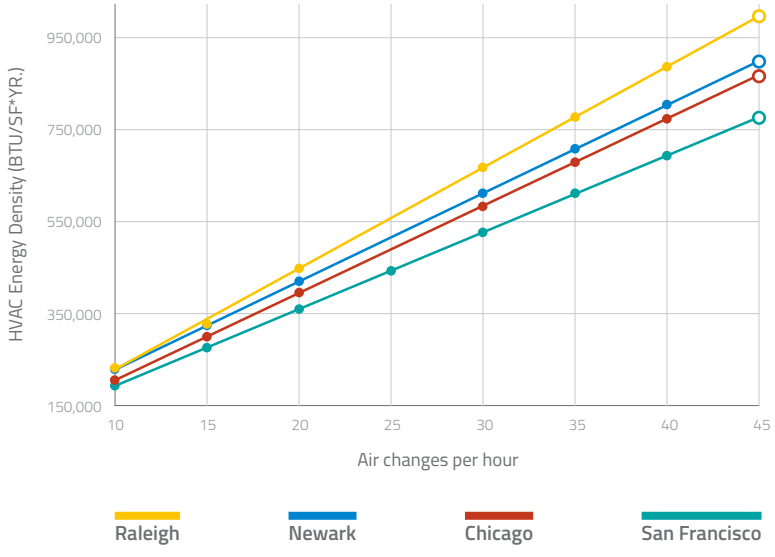
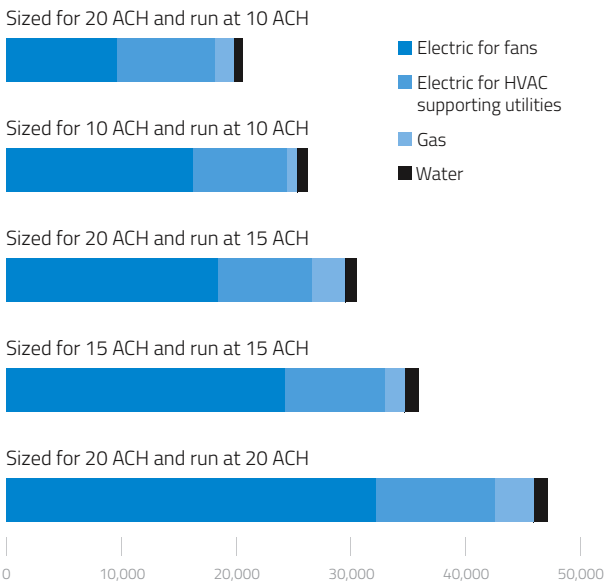


FIGURE 3

Energy cost vs. air change rates and AHU sizing



Sizing in the table above does not show the added 10 percent margin to ensure the system meets the sizing airflow listed.

standpoint when considering running an air handling system at a lower airflow rate. The following modifications may be needed for lower air change rates:

- Coil and humidification control valves turndown;
- Confirm venturi air valves do not fall below their minimum allowed airflows;
- Balancing valves may need to be reduced in size to get adequate velocity to allow for balancing;
- Airflow may be needed for pressurization such as bubble airlocks limiting the reduction in airflow;
- Review part load operating conditions of central utility systems.

Various energy codes make explicit restrictions on oversizing air handling systems. Examples include the International Energy Conservation Code 2015, which states: "The output capacity of the heating and cooling equipment shall be no greater than the loads calculated." Typical HVAC systems for pharmaceutical cleanrooms use chilled water and heating hot water that are impacted by reducing the load on the systems.

Based on our analysis, systems designed for higher airflow rates, but running at lower airflow rates can generate the biggest savings for pharma facility operators. However,

consideration needs to be given to all aspects of the system to ensure there are no potential design and operational issues with a system running at a lower airflow rate.

Conclusion

Energy costs associated with HVAC can account for over 60 percent of a pharma GMP facility's energy use and cost. Large portions of this cost are from cleanroom HVAC systems. Typically, air change rates for clean spaces are based on historical data, leading to overdesign, which increases utility costs and carbon footprint.

However, using a safe but adequate airflow that allows for compliant operation, while at the same time minimizing utility cost, carbon footprint and resource waste, is beneficial for facility operators and society in general.

Oversizing an air handler and operating at a lower airflow than design saves more energy than creating and operating at a lower airflow rate while reducing the risk of being undersized to properly maintain room particle counts. Based on the analysis, energy savings can be as much as 30 percent lower with the same operating airflow.

Energy savings for multiple units add up as air change rates are reduced. Multiplying these savings across a campus will have a significant impact on site utility consumption. Sizing systems for reduced air change rate will not allow for adjustments in air changes to meet regulatory particulate requirements, if it becomes an issue.

Reduced airflow rate can delay the start-up of a facility and require significant facility modifications to correct. An alternative is to size an HVAC system to ensure compliance and then back the airflow down as the system and space classification will allow. Energy codes may not allow oversizing HVAC systems, so there is a need to communicate with the relevant authorities. With adequate information showing energy savings with an oversized system, an exception could be granted.

References

See pharmamanufacturing.com for a complete list of references.

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An easier pill to swallow

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

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 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

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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.

Successful OSD projects demand strong foundations to be laid during the initial stages.

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 translate into using multivariate models to integrate "coating by trend" into the control strategy for the product; even to allow endpoint 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.*

product focus

Meagan Parrish
Senior Editor

The surge of single-use

Emerging one-and-done solutions for pharma

The rise of single-use technologies (SUT) in pharma has shown no signs of abating and is continuing to transform every area of operations.

"The global single-use bioprocessing market was valued at $12.6 billion in 2019 and is projected to witness a CAGR of 12.8 percent by 2027," says Mark A. Sitcoske, CEO of High Purity New England. "SUT continues to experience huge growth in 2020 in pre-commercial manufacturing, including preclinical and clinical scale systems for upstream processing, such as single-use media bags, bioprocess containers and mixers."

In addition to preclinical applications, pharma is turning to one-and-done equipment to reduce manufacturing risk, time and costs, while boosting needed flexibility for the production of next-generation therapeutics. In response, vendors have continued to innovate SUT solutions that improve productivity throughout all areas of manufacturing — from sample testing to tracing products after they've been shipped out the door.

Sampling advanced therapies

With the rise of novel cell and gene therapies, the biopharma industry has turned to SUT to solve some of the challenges with small-batch manufacturing.

"Single-use products and systems are already proven as flexible, cost-effective alternatives to traditional bioprocessing methods when it comes to the production of monoclonal antibodies (mAbs)," says Timothy Korwan, director, New Product Introduction for single-use solutions, Avantor. "As a result, the ingenuity of single-use may also be adopted to improve cell and gene therapy production processes."

According to Korwan, the frequent in-process sampling for cell and gene therapy production make SUT an attractive option for reducing the risk of contamination and preventing product loss. To that end, Avantor recently launched a single-use closed-system sampling solution: OmniTop Sample Tubes Adjustable Volume Sampling System.

Ideal for high-integrity product sampling applications such as mAbs, cell and gene therapy processes, and final fill operations, the system offers a unique dip tube with an integrated adjustment tool, which allows technicians to move the dip tube to the corresponding collection volume. Ultimately, the company says the system lowers contamination risk and reduces volume loss by enabling technicians to collect the exact amount of product needed to perform routine sampling or for a specific analytical process.

Avantor's OmniTop Sampling System (AVSS) standardizes the bioprocessing sampling process.

Mixing it up

Reducing contamination has also been a driver behind the transformation of mixing innovations to SUT.

"The industry has progressed toward using single-use bag technologies rather than traditional methods of stainless-steel tanks and grades A/B processing because of the positive characteristics they offer to end users … [such as] eliminating the risk of cross-contamination and reduced cleaning time," Sitcoske says.

According to Sitcoske, High Purity New England (HPNE) developed its ClearMixx system to meet the growing demand for a more accurate single-use mixing solution.

"ClearMixx offers rapid and completely homogenous mixing for your process — without any impellers or moving components," he says.

Designed to perform liquid/liquid and powder/liquid mixing, with a dispersion plate able to efficiently mix the most challenging buffer, media, and biopharmaceutical ingredients, ClearMixx is also able to keep API suspended during fill-finish.

Advanced materials

Leveraging advanced materials is another way that SUT can be enhanced to further limit contamination risks.

"One materials-based solution that can address particular bioprocessing challenges is the use of fluoropolymers, particularly a polymer such as polytetrafluoroethylene (PTFE)," says Keith Fritsky, product specialist at W.L. Gore PharmaBIO. "This substance has favorable chemical properties. It is bio and chemically inert, with a low coefficient of friction. It is chemically stable and non-particulating, with low extractables and high levels of purity."

Gore's LYOGUARD Freeze-Drying Trays designed for API lyophilization incorporate an innovative high-moisture vapor transmission rate ePTFE membrane that helps protect products in the tray, and deliver a high-vapor transmission rate, so water and solvent vapors are readily released.

According to Gore, the single-use trays solve a time-consuming problem of product ejection and spillage often associated with the use of stainless steel. The new trays are ideal for bulk freeze-drying a variety of drug substances like polypeptides, oligonucleotides and other APIs or HPAPIs.

SpotSee's ShockWatch RFID improves visibility throughout the supply chain.

HPNE's ClearMixx utilizes a low sheer single-use Quattroflow pump chamber.

Traceability

SUT can also be leveraged to overcome challenges related to track and trace, which continues to be a major focus for pharma.

"From serialization to product tagging, companies are continuously looking for ways to gain more insights into the supply chain," says Angela Kerr, vice president, Product Portfolio, SpotSee.

SpotSee's ShockWatch with radio-frequency identification (RFID) technology provides a single-use, tamper-proof device that combines traditional RFID inventory management with impact-damage monitoring to help deter, detect and diagnose issues throughout the supply chain. The company says that by gathering data throughout the supply chain, ShockWatch RFID helps users quickly identify where damage is occurring and isolate damaged inventory for further inspection.

"RFID technology has already helped companies reduce inventory management costs by seamlessly automating asset identification," Kerr says.

All told, Fritsky says that SUT is continuing to help pharma usher in a new era of advancements.

"Bioprocessing is at a threshold — a threshold in which emerging technologies can help realize the vision of the industry to push beyond what is possible while also creating operational efficiencies that provide real benefits," Fritsky says.

Peter Walters
Lead Process Engineer, CRB

Don't pigeonhole your viral vector production

The top three design considerations for flexible ATMP retrofit

If your organization is planning to create capacity for advanced therapy medicinal products (ATMP) or viral vector production, there are three key engineering considerations to take into account: Facility current good manufacturing practice (cGMP) flows, base efficiency and airflow control. These considerations are relatively easy to underestimate, because in many ways the technology behind viral vector production seems similar to production of monoclonal antibodies.

If your production requirements are higher than your available square footage, and a new build is not an option, design becomes a balancing act. You'll need to come to grips with what you can sacrifice and still meet your original production goals, and ensure that any retrofit will not pigeonhole your facility's future capabilities.

Facility flows

Historically, cGMP flows were about mitigating adventitious virus, whereas in viral vector manufacturing, we can't avoid viruses or vectors, because that's the product. But the facility design needs to account for viral vectors differently than in mAb production.

Testing surfaces and the environment to ensure that you're not getting carryover nascent viruses from a previous process is not something that was considered previously. Today, you're not just mitigating against whatever environmental virus gets floated into a room when people walk through; you are actually manufacturing viral vectors in the billions. How to design a facility around controlling this viral vector load is worth understanding in detail. Consider:

- How are you ensuring that the vectors you're working with don't escape equipment into the environment?
- Have equipment manufacturers given you enough specification data to know if you're exposed to a potential problem?
- How are you ensuring that you're mitigating any possible escape of material with room design and decontamination procedures?

Your facility should have a strict cGMP flow design because of uncertainty around the containment of manufacturing processes. There are specific design criteria and equipment that engineers can recommend to mitigate risk, on a case-by-case basis.

Careful upfront planning, including modeling flows for further optimization, determining decontamination procedures to mitigate vector exfiltration, and understanding all available equipment and design options are critical.

Base efficiency

Vector technology expansion projects leverage a lot from the mAb space. People often think that because the technology looks familiar, the demands are the same. Consequently, they underestimate the square footage required for a multiproduct high-throughput facility.

If you're starting with a facility that was designed around a throughput for a single product and now is being retrofitted for a range of products, ask yourself: What is the anticipated production requirement for every product? And, do we have the square footage to accommodate the equipment itself?

Often, companies can campaign between product lines throughout the year. In other cases, they may need multiple rooms because production requirements make sharing rooms impossible. As production expands, even more square footage is needed for required segregations.

Airflow control

Now that you're producing viral vectors, how do you ensure that they aren't spreading throughout your facility? Some process steps create the opportunity for particle aerosolization. You must ensure those aerosolized particles aren't free floating through your HVAC system into adjacent spaces.

How does your design accommodate appropriate levels of air changes per hour? Which rooms do you zone together, and which are single pass? How do you handle pressurization considerations to maintain boundaries for where viral vectors are manufactured and contained? There are experts for whom these questions are more commonplace and the answers more nuanced. Ask these and every other possible question .

We might see facility flows, base efficiency and airflow controls become better understood in the future, as viral vector technology is improved. For now, understanding the basics of these design considerations will allow you to properly set up your facility to take on your new lines of viral vector business.

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Never too small to think big

Up-front design considerations can improve long-term processing flexibility

You may not be thinking about the future scale-up to commercial production when you're in the early stages of crafting a new biologic therapy. And yet, the early design choices you make in your single-use facility can greatly affect your speed to market and ability to prove regulatory compliance. These decisions can also impact your production flexibility for future growth.

Securing FDA approval may prove more cumbersome if processing data is not automatically collected. And if your equipment isn't designed to communicate between units of operation, setting up for production runs is an onerous process.

For these reasons, you're never too small to think big when it comes to your manufacturing ecosystem. By addressing future needs early with smart process design, you can scale your operations from development to production with minimal disruption, and be better prepared for future products and expansion.

Design your risk out

Consider the challenges that can arise in a single-use process that's not designed for long-term production needs.

Most likely, your manufacturing process is a hybrid of unit operations that use multiple software platforms and don't effectively talk to each other. As a result, operators will need to manually configure each asset before a production run. Technicians will also need to work with several vendors to maintain the assets. And IT personnel will need to support, update and patch the software platforms all separately.

Meanwhile, when equipment isn't integrated, it's difficult to automate data collection across platforms. As a result, operators may need to manually collect data from each asset, and reformat the data if different assets produce it in different standards.

All these manual steps and equipment disparities can create tremendous potential for mistakes, and make changeovers and review times inefficient and lengthy. And they can result in gaps that can compromise your data integrity and complicate regulatory approvals.

Design ingredients

How do you design your single-use manufacturing process for your long-term compliance and production needs? Consider these key elements:

A common network protocol: A standard protocol allows you to connect your disparate production assets so they can share data and run as a cohesive system.

EtherNet/IP, for example, is a widely used protocol in industrial environments and time-critical applications. It allows secure, real-time information sharing between equipment, systems and enterprises.

A standard equipment platform: When you use standardized instead of customized equipment, you help operators work more efficiently with a common interface. Whether they're working on a bioreactor, filtration skid or purification skid, they get the same look and feel across assets. Maintenance technicians only need to work with one support provider. And IT personnel can worry less about maintaining and securing different systems from multiple vendors, which can help reduce costs and potentially reduce security risks.

Automated data collection: Using a batch historian to automate your data collection will save time in the long run. It can also lower the likelihood of errors, and offer fast, easy access to data to help speed up reviews and regulatory approvals.

A historian can also help you manage quality. When combined with analytics software, it can help you identify issues like temperature excursions as they happen, rather than months later when you pour through data. And because your data is centralized, you can easily put insights into reports and share them with others in your organization.

A scalable architecture: Adding additional equipment can be a challenge if flexibility isn't in the initial design. The equipment must be accounted for in recipe management, unit allocation and data-collection systems. If a standardized, integrated approach isn't taken in design, custom SOPs and batch records for each new piece of equipment may be required.

By thinking long term about your single-use manufacturing, you can optimize your drug-development efforts today and accelerate product releases in the future.

Having the vision and planning to enable future possibilities takes a little effort in the initial stages but can pay off in huge dividends in the long run.

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