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Editor's Message

LOOK FOR US ON

Efficiency: One Step at a Time

I like to think that in a previous life (or maybe in a future life) I was an efficiency expert.

Set out a couple of tasks for me, or a couple of errands, and I like to figure out how best to approach them – what's the best route, what will entail the least effort, what's easiest.

But I guess most people are like that. Who wants to waste time or effort if you can be more efficient?

For many years, the pharmaceutical industry was rather inefficient.

But who could blame them? When profits are high, it's ok to be inefficient – especially in your manufacturing operations. Furthermore, if your process is running and the FDA has approved it – why fix something that, technically, isn't broken and open yourself up for another round of inspections?

The short answer is no one did it. If you were pumping out enough product to meet demand and financial goals – no one was really concerned if a batch or two was out of spec. Just toss it – and make more.

But, time marches on, economics change, and manufacturing efficiency is now the big game in town.

Perhaps the biggest advancement in manufacturing efficiency has been the introduction and ongoing refinement of continuous processing. Continuous processing technologies allows manufacturers to eliminate the stopping and starting of processes as material is moved from one step to another. Less steps means more efficiency.

Efficiency improvements have also found their way into the drug discovery arena – companies are now using advanced data analytics to predict which compounds have the best chances of success. The mantra of "Fail early" is a good one. Eliminate the less promising compounds and focus on the most promising products.

And, of course, the COVID-19 pandemic has shown us other ways to be more efficient and improve processes.

Decentralizing clinical trials and making them more "virtual" shows promise and is an ideal way to make sure clinical trials move along as planned.

Virtual vendor visits are supplanting in person visits. While due diligence has to be done, in a socially distancing world, where projects have to move forward, a video tour/audit can be an efficient way to start a vendor/client relationship.

Finally, supply chains need a good looking at. If anything, the pandemic has shown that supply chains are more fragile than we thought, and the longer the supply chain is – the more likely problems will arise.

Efficiency will come. But, as with most change – it will come one step at a time. The key is to make the most out of each step and not waste any effort.

Mike Auerbach
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From the Cover

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CNPerspectives

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Pharmaceutical Outsourcing is one of several outstanding publications available from CompareNetworks, Inc. Here is a look at the insightful content our readers may enjoy from four of our sister resources: *American Pharmaceutical Review*, Biocompare, Labcompare, and Dentalcompare.

Fluidity Versus Certainty in Early Small Molecule CMC Development

American Pharmaceutical Review

The transition of a drug from optimized medicinal chemistry lead to candidate nomination and development through clinical proof of concept has been referred to as the "Valley of Death." It is the most consequential, high-risk period in a drug's development. A relatively recent assessment indicates that the average success rate of development candidates in this portion of the drug development cycle is ~30%.4 During this interval, basic science knowledge needs to be translated into practical application in a clinical setting. Translational research is the means by which the shift is made from basic to applied science. It has been stated that the *"main objective of translational research is to make sure that the discoveries that advance into human trials have the highest possible chance of success in terms of both safety and efficacy in human studies."* This is an increasingly high bar to surmount.

https://bit.ly/3kUVyB9

Improving Drug Discovery with Organoids

Biocompare

Discovering an approved drug that effectively prevents, mitigates, or cures a particular disease can be a protracted process that requires multiple screenings of tens of thousands of compounds prior to clinical trials. Despite rigorous assessment, the majority of these potential drugs, around 80%, fail clinical trials. Effective cancer drugs are even harder to come by, with an estimated 95% or higher of compounds unsuccessful at the clinical trial phase. Why such high failure rates? Sometimes drugs are unsafe for humans, but most of the time, they are simply ineffective. It has become clear that many cell- and animal-based models are not predictive of clinical efficacy, especially when dealing with heterogeneous diseases, such as cancers. There are multiple parts to a drug screening system. There is the compound or drug, the model in which it is being tested, and the readout.

https://bit.ly/3hhflIM

High Resolution Ion Mobility in Today's Pharma and Clinical Research

labcompare

As the current COVID-19 crisis has revealed, uncovering the deep secrets of clinically significant molecules is absolutely critical for developing effective treatments and therapies. We identify the usefulness of testing and laboratory instrumentation by the depth of the resolution these instruments can achieve. Throughput, ease of use and speed are also important, but resolution – being able to see deeply into the unseen – of whatever clinically significant molecule is important to that researcher, is paramount. If we could dramatically improve the resolution of such instrumentation, imagine how profoundly that could affect the pharmaceutical industry, clinical research and patient care. Now, imagine that the same technology that allows for such an industry step change could reduce reliance on typical labor intensive traditional methods and works instead on computer printed circuit boards. After all why hasn't more laboratory instrumentation moved into the Digital Age?

https://bit.ly/3haiz0Q

6 Tips to Help Dentists Get Through the COVID-19 Pandemic

dentalcompare

It is certainly anything but business as usual for dentists all over the world. The ongoing COVID-19 health crisis has sent dental practices into a tailspin as they race to shift their business model to meet the needs of patients while still being responsible global citizens.

Yes, these are challenging times, but remember you're not alone. We're all trying to navigate through the COVID-19 pandemic. Here are six important tips to help you get through it.

https://bit.ly/315qEOK

Social Media Connections

CDC_eHealth
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@FDA_Drug_Info w/ @CPathInstitute & @ncats_nih_gov recently launched CURE Drug Repurposing Collaboratory – a new component of the CURE ID App – to accelerate identification of new uses of current drugs to potentially treat diseases including #COVID19: https://bit.ly/3gcX7ap

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Did you know that 70% of your immune cells reside in your colon? Your gut health plays a key role for a healthy #immunesystem. Find out more about the #HumanMicrobiome and its role for your health.

FDA Drug Information
@FDA_Drug_Info

#FDAapproves new treatment for neuromyelitis optica spectrum disorder (NMOSD), a rare autoimmune disease of the central nervous system that mainly affects the optic nerves and spinal cord: https://go.usa.gov/xfe7m

Sandoz
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#Biosimilars can fill an important unmet need by providing expanded options, enhanced sustainability for health systems and increased access to therapy.

IBM Watson
@IBMWatson

Many believe COVID-19 may have escalated the pace of #AI adoption and integration. Learn how virtual agents such as Watson Assistant are helping businesses respond during the pandemic: https://ibm.co/31NXfHY

Sanofi US
@SanofiUS

Vaccinations can help protect teens against meningitis, whooping cough and other illnesses, especially during this critical period of growth. Check out the @CDCgov's resources for parents here: https://bit.ly/3kKnwjc #NIAM20 #ivax2protect

Deloitte
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Exceptional circumstances, such as those of #COVID19, require a blend of courage, clarity, and humility.

American Heart Association
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Research shows those living with #diabetes #heartdisease are at increased risk from severe coronavirus complications. Learn more and take control at http://spr.ly/6019GZGwR. #Type2Take2 Founding Sponsor @novonordiskus

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Adjusting to a New Normal in API Manufacturing

Seven Observations that Can Help Keep Operations Running Smoothly During the Pandemic

Ed Price
President
Seqens North America

COVID-19 continues to take a toll at home and in business. As companies everywhere work to adjust to a new way of working, those of us in the Contract Development & Manufacturing Organization (CDMO) world may have an advantage. As essential work, many of us have maintained ongoing on-site operations, and as chemical manufacturers, we have always been committed to strict cleaning guidelines.

Nevertheless, to remain open, and for the safety of employees, we've had to rethink basic processes – from handwashing and wearing face masks beyond the GMP suite, to eating in the cafeteria and holding client meetings. New protocols and Standard Operating Procedures (SOPs) will continue to unfold as we adjust to the new working normal, but below are a few observations and lessons learned that can help us make the adjustment just a little easier.

1. Employees remain the lifeblood. Chemists, project managers, QA teams, admin staff and all employees remain the lifeblood to the success of a CDMO. These are unprecedented times and not only do we need to make sure employees stay home if they are experiencing any symptoms, but we also need to be empathetic to their concerns and situations. For any employees working remotely, it's critical to maintain ongoing communication and collaboration and reinforce the valuable role they provide.
2. It's easier than ever to connect with sponsors. In API manufacturing, it's vital that CDMOs connect with their sponsors, maintaining regular update meetings and collaborating when issues arise. Surprisingly, getting in touch with sponsors is now easier than ever. Many sponsors are working from home offices and video calls or even the old-fashioned phone call can get a lot accomplished in a short amount of time, without the hassle of trying to coordinate schedules for in-person meetings.

***Ed Price** is President and CEO of Seqens North America (formerly PCI Synthesis), an integrated global provider of pharmaceutical synthesis and specialty ingredients. From the company's Newburyport, Mass. operations, Seqens N.A. provides emerging and mid-sized pharmaceutical companies access to the expertise needed to develop and manufacture complex small molecules.*

3. The decline in on-site visits requires ingenuity. While ongoing communication with sponsors has improved, unfortunately on-site visits from potential new sponsors has declined because of travel bans and stay-at-home guidance. Before COVID-19, prospective sponsors required facility audits to make sure CDMOs had the capabilities, equipment and people needed to handle their projects. Today, CDMOs need to create new ways to attract new sponsors, through videos, virtual reality and other technologies that can help sponsors experience the site virtually.

4. Cleanrooms have taken on new meaning. Cleanrooms designed to remove pollutants, particles and contaminants in GMP manufacturing have always been a way of life. Here at Seqens NA, there are three things that we are diligent about maintaining in order to ensure cleanrooms: control and quality of the air, internal surfaces, and equipment. We have strict, validated protocols in place for cleaning GMP suites in between each project; we conduct regular monitoring and testing and we're recertified annually. Cleanroom staff are specifically trained for these environments and they wear protective clothing designed to trap contaminants that are naturally generated by skin and the body. This expertise and understanding of viral transfer can be applied across the organization and help inform protocols for where people congregate, how surfaces are cleaned and what protective equipment may be needed – beyond the GMP suite or cleanroom.

5. Sticking to a schedule is more important than ever. In times of fear, uncertainty and change, sometimes sticking to regular routines and schedules can be a welcome distraction. This fact makes a CDMO's environment quite welcoming when it comes to a pandemic. CDMOs live by SOPs, protocols and strict project schedules and maintaining these rigorous routines just may be the key to keeping business moving full steam ahead.

6. Pandemic shines a spotlight on our overreliance on overseas supply chains. Due to travel bans, border closures, and shelter-in-place measures that are being enforced around the world, it has become glaringly evident that our reliance on China and India for drug products, APIs and raw materials is bordering on the dangerous. In fact, it's estimated that pharmaceutical companies in India "supply about 40-to-50 percent of all U.S. generic drugs." Perhaps the pandemic will be the catalyst to government and private action to bring manufacturing back to the U.S.

7. Pivoting may be a new protocol to success. While API manufacturing continues to be in high demand as sponsors look to bring vital drugs to market, there are other ways that CDMOs can lend their expertise to assist in responding to the pandemic. For example, understanding that businesses have been challenged with getting supplies of hand sanitizer to employees because of supply chain disruption and a shortage of the raw material Isopropyl Alcohol (IPA), Seqens got to work manufacturing hand sanitizer. We followed the chemical formula recommended for hand antisepsis against coronavirus, by the World Health Organization (WHO).

The coronavirus is creating mayhem across the world, but the silver lining is that many CDMOs are realizing just how resilient they can be when faced with adversity. Sticking to best practices that have always been the hallmark of CDMOs, focusing on employees and customer communication and being willing to change course as needed, will be the keys to success and continued innovation that bring critical drugs to market.

Biologics CDMO Trends and Opportunities in China

Rapid Growth of Domestic mAb Pipeline and Regulatory Reform is Creating Business Opportunities for Biologics CDMOs in China

Vicky Xia and Leo Yang

BioPlan Associates, Inc.

Both multinational and domestic Contract Development and Manufacturing Organizations (CDMOs) are striving to enter this new segment in China. The recent regulatory reforms, and the potential opportunities are creating an upswell in investment and interest. BioPlan's research for its Top 100 Biopharmaceutical Facilities in China Directory now show (http://www.top1000bio.com/top60china), there are well over 100 biopharma companies in China, both new and established, that have started mAb development projects.[1] Many of these product innovators have limited experience in actually manufacturing a biologic, so, as with Western innovators, they are increasingly turning toward CDMOs.

Boehringer Ingelheim was the first multinational CDMO to test the water in China in 2016, and due to growth in demand, in 2019, it announced plans to expand its capacity. Lonza, the global giant in the CDMO industry, made a strategic move to enter China at the end of 2018. Korea-based Celltrion also announced plans to build a bioproduction facility in Wuhan in 2019. Dozens of domestic companies, existing CRO companies as well as brand new start-ups, kicked off their biologics CDMO business as more biosimilars and innovative mAb therapeutics began entering the clinical pipeline and reaching commercial scale.

Since the successful launch of Langmu in 2013, Chinese developers have submitted IND applications for 109 Class I biological therapeutics, including 61 therapeutic mAbs, nine ADCs, four bi-specific antibodies and one PD-L1-Fc, as well as 26 recombinant proteins, 13 fusion proteins and a number of gene therapy products, therapeutic vaccines and oncolytic viruses.[1]

In Table 1 we can see the launch of mAbs into the China market has clearly picked up pace in recent years, with 2019 alone witnessing seven mAb therapeutics from domestic developers getting NMPA's approval to be on the market, a record high number for a country which approved its first made-in-China mAb therapeutics beginning in 2005. Such a trend is likely to continue, as multiple industry insiders project that China may be home to five to ten new mAbs annually within the next five to ten years, creating greater demand for the biologics CDMO industry.

As most early-stage biologics developers in China lack manufacturing facilities, the need for contract manufacturing services would be certainly on the rise. As part of this market environment, total capacity in China has grown by over 10%, based on our analysis of facilities under active construction. BioPlan's Top 100 Biopharmaceutical

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Table 1. mAbs from Domestic Developers Launched in China[2]

Company Name	Project Name	Time of Launch	Revenue Information
Bio-Thera Solutions	Adamulimab biosimilar	Launched in 2019	NA
Shanghai Henlius Biotech	Herceptin (trastuzumab) biosimilar (HLX-02)	Launched in 2019	NA
Hisun Pharma	Humira (adalimumab) biosimilar	Launched in 2019	NA
Innovent Biologics	IBI-308, PD-1 mAb	Launched in 2019	USD $48 million in 2019 H1 (financial statement)
BeiGene	BGB, tislelizumab, a PD-1 mAb	Launched on Dec 2019	NA
Qilu Pharma	Avastin (bevacizumab) biosimilar (Qilu)	Launched on Dec 2019	NA
Shanghai Junshi Biosciences	JS-001, a PD-1 mAb	Launched in 2019	USD $44 million in the first half year of 2019
Hisun Pharma	Enbrel (etanercept) biosimilar	Launched in 2015	USD $26 million in 2018
Kanghong Pharma	Langmu (conbercept), a Lucentis biobetter	Launched in 2014	USD $126 million in 2018
Celgene Shanghai	Enbrel (etanercept) biosimilar (Qiangke)	Launched in 2011	NA
BioTech Pharma Beijing	Taixinsheng (cancer mAb)	Launched in 2009	USD $23 million in 2009, increased significantly to USD $141 million in 2018 after getting into NRDL
3S Guojian	Enbrel (etanercept) biosimilar (Yisaipu)	Launched in 2005	Over USD $140 million in 2018

Source: China Biologics CMO Report, June 2020, Bioplan Associates.

Manufacturers in China (http://www.top1000bio.com/top60china) directory shows continued capacity expansions and upgrades at a majority of biomanufacturer facilities through 2019.[1] But growth of the biologics outsourcing services market is even more significant, with projected CAGR over 30% for the period 2016-2021 (Figure 1).[2]

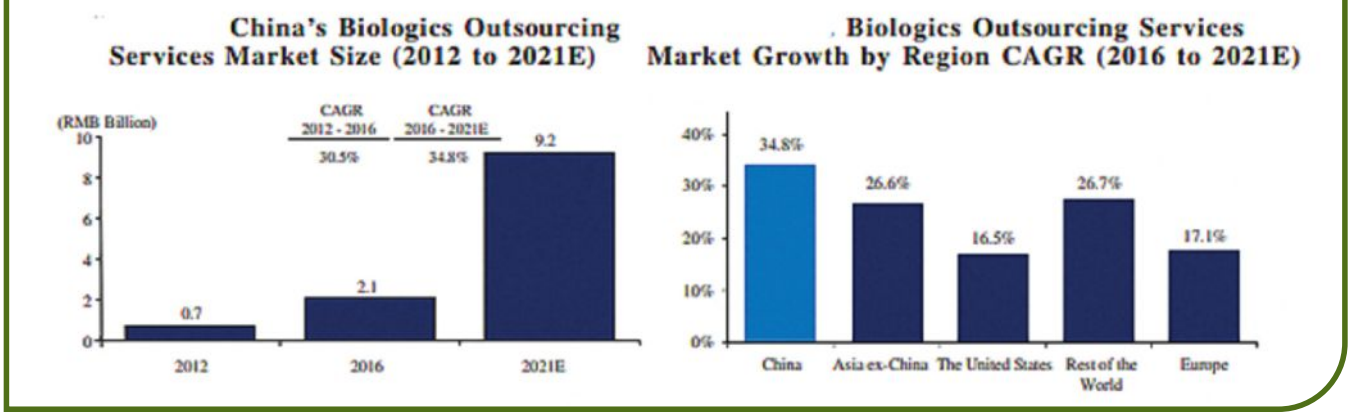
Regulatory reforms are crucial for the growth of China's biologics CDMO industry. With both global and domestic demand on the rise, Chinese regulatory authorities made the move to permit contract bio-manufacturing in China in 2016. That year, China started the pilot Market Authorization Holder (MAH) program, under which holders of a CFDA biologics approval number now have the option to either manufacture the drugs or use a CMO. The MAH breakthrough is a pilot running in ten provinces and municipalities, and at the end of 2019, the updated Drug Administration Law removed regulatory hurdles for contract manufacturing of drugs in China (vaccines excluded). Both domestic developers and CDMOs hope there will be future reforms which would make outsourcing of bioprocessing an easier decision.

At the current stage, it is still mandatory that DS (drug substance) and DP (drug products) have to be manufactured at the same place, which makes sub-contracting difficult to operate. In 2020 with the COVID-19 pandemic, some industry insiders also think it is possible that NMPA will make contract bioproduction of vaccines legal in China in the future in a move to speed up innovative vaccine development amid increased public awareness of public health issues.[3]

Commercial Scale Contract Bioprocessing Has High Growth Potential, But Developers Still Have Strong Preferences for In-House Facility

Many analysts are curious about whether commercial scale outsourcing of bio-production will be more mainstream in China, as it is the key factor for growth of the biologics CDMO industry with typical service revenue at dozens of times that of early stage clinical manufacturing (USD $50-100 million annually versus USD $4-6 million in 3 years)[2] while most of China's biologics CDMOs only have clinical scale bioprocessing deals at current stage.

Figure 1. Growth of Biologics Outsourcing Services Market in China[2]



Though China's MAH reform since 2016 has opened doors for commercial scale contract manufacturing, domestic developers still have a strong preference for in-house commercial scale bio-facilities. The most important factor behind this preference is cost concern. As most of the mAb pipeline under development by domestic companies are of bio-similar/me-too nature, the projected profit margin would be significantly less than that of mAb therapeutics originated from MNC pharma. While outsourcing of clinical scale bioprocessing is a common strategy to speed up development by domestic companies, especially the start-up biotech companies, outsourcing of the whole manufacturing process is widely regarded as too expensive. The CDMOs prefer single-use technology while many biopharma developers use stainless steel bioreactors for commercial scale production as it costs less in the long-term.

Until recently only the industry leader WuXi Biologics has been widely accepted by the industry as fully capable of commercial scale bioprocessing, and many of the developers would not be able to use WuXi's services at commercial scale. There is also concern of loss of control over the manufacturing process. The current regulatory system puts the market authorization holder as fully responsible for the products over the whole life cycle, so developers tend to be very cautious in outsourcing the whole of bio-manufacturing work to a CDMO due to quality concerns. Many of the VC/PE groups behind the mAb developers would need the company to go public as an exit route, and Chinese investors are known for their preference for fixed assets such as land, factories over intellectual property such as pipeline, patents, etc. Such a preference has made many domestic developers to view building an in-house bio-production facility as a strategy to get high evaluation via IPO.

Up until 2019 it has also been relatively easy for mAb developers in China to get resources for building an in-house facility. Enthusiasm of investors give high evaluation of companies while municipal governments can help developers with access to bank loans and cheap land. As a result, few domestic developers have turned to external partners for commercial scale bio-manufacturing. Even BeiGene, the first partner with Boehringer-Ingelheim's facility in Shanghai, the pushing hands behind the MAH reform, in bio-production of its PD-1 mAb, started its own commercial scale bioprocessing facility in Guangzhou. Up till now BioPlan's internal studies only find four commercial scale contract manufacturing deals with China-based CDMO, among which three are with WuXi Biologics.[2]

WuXi Biologics financial statement also shows that late-phase (phase III) and commercial manufacturing is only ~7% of its projects, with only one product in commercial manufacturing in 2018. While in the first half of 2019 we witnessed the number of late-phase (phase III) projects of WuXi Biologics increasing by 50% from ten as at same period last year to fifteen as of June 30, 2019, commercial manufacturing deal shows no growth (only 1 deal).[4]

Some industry insiders think a made-in-China mAb will most likely remain a low profit margin product which would make outsourcing of commercial manufacturing a very difficult decision, as the most recent NRDL (national reimbursement drug list) negotiation shows that policy makers want to force mAb developers to increase revenue at the expense of profit margin. Sintilimab from Innovent Bio, the only PD-1 mAb to get listed into the NRDL, had to reduce its price by ~64%.[2]

However, not everyone is that pessimistic. Some CDMOs think the current slow growth of commercial scale outsourcing may be simply due to the fact that the wave of BLAs for mAb therapeutics is just beginning to arrive in China and there are few commercial scale bio-manufacturing projects of mAbs to begin with. With the newly updated Drug Administration Law which gives a higher penalty to developers who violate quality requirements, developers of mAbs which do not have enough technical expertise in bio-manufacturing may have to seek help of an external partner for commercial scale production. There is also a trend of investment in mAb therapeutics cooling down in China, as witnessed by less deals in 2019 than in previous years. Municipal governments are also running out of funds to support every mAb developer in their region to build in-house facilities. Instead they may turn to the strategy of supporting a commercial scale manufacturing platform which can provide contract manufacturing services to multiple developers. Chinese investors' preference for fixed assets over intellectual property may also change and if the pipeline itself can translate to a high evaluation investors would not insist on building in-house facilities, giving more growth opportunities for commercial scale contract bioprocessing. As over 30 mAbs from domestic developers are already at the Phase III stage, it is safe to project that China will need an additional capacity of 100,000L or more annually in the near future, which could translate to more business opportunities for biologics CDMOs.

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Leo Cai Yang, Project Manager, BioPlan Associates, has business development experience in biotech and pharma segments and 10 years in market research. He graduated from East China Normal University with a bachelor's degree in Biotechnology in 2006, and has worked with equipment manufacturers in pharmaceutical and medical device industries, in Switzerland, Austria and Germany. He has also project managed studies involving new biopharmaceutical technology applications in China including analysis and strategy development.

Pre-Filled Syringes: Development Challenges and the Value of Partnership

Anish Parikh

Vice President, Drug Product Sales & Marketing
AMRI

Highly efficacious, innovative medicine needs cutting edge delivery systems to match, and pre-filled syringes (PFS) are stepping up to the plate.

The PFS space is one of the fastest growing sectors in pharma, expected to be worth $9.7B by 2025,[1] thanks in part to their greater patient safety profile and lower manufacturing costs.

But pre-filled doesn't translate to easily filled. The increase in biologic drugs, which has been driving the PFS boom, presents particular obstacles, and there's no one size fits all approach.

In this article, we will chart the rise of the PFS, outline some common challenges, and explain how partnership is the only route to success.

The PFS Boom

Driven by the trend toward biological medications, the PFS space has seen huge growth in recent years.

This new breed of "living" medicines, made possible by rapidly evolving technology and an ever-greater understanding of the underlying mechanisms of disease, has proven to be nothing short of life-changing for people living with long-term conditions.

Administering these medicines, however, presents a challenge. High levels of gut degradation rule out the oral route, meaning they must be delivered parenterally.

PFS has emerged as a more suitable method than traditional needles and vials for a number of reasons. It is better suited to emergency situations and remote areas, for example, and is ideal for the self-administration required for the delivery of many monoclonal antibodies used in long-term conditions.

They also can reduce costly dosing errors by facilitating the provision of exact doses and help boost medication compliance thus helping people to avoid negative health complications. Crucially, the level of pressure needed to inject highly viscous biological products makes the use of vial-based syringes extremely challenging in the burgeoning realm of self-administration.

Put simply, the PFS and biological medicines booms are happening at the same time because the two are intrinsically linked.

As many "first wave" biological products reach the end of their patent period, biosimilars are increasingly entering the marketplace. Since 2016, more than 50[2] have come on-line and many more are in the pipeline.

In addition, the extraordinary potential of gene and cell therapies is beginning to show its hand. Clinical trials suggest that cell therapies could revolutionize cancer care, and that gene editing may even be able to, for example, reverse blindness caused by specific genetic mutations.

In 2018, the FDA had 500 active investigational new drug applications involving gene therapy products, and $2.3B in funding has been pumped into private gene therapy companies over the last 10 years.[3]

Such innovative products will need cutting-edge, patient-centric administration systems. And as medicine stands ready to take its next giant leap forward, PFS stands ready to deliver them.

Patient-Led Design

While the synergy in the rise of biological medicines and PFS is clear, the relationship between product and delivery system is fraught with challenges. We must remember that PFS are not all-purpose vessels, and that selecting the right design is not a straightforward process.

Each complex protein or peptide has a unique formulation and will differ in use and safety profile. It means that each individual product requires custom manufacturing, sterilization, filling, and compliance procedures.

When designing these processes, PFS professionals must consider a wide range of factors, such as the product's efficacy, active pharmaceutical ingredients (APIs), characteristics and safety profile – as well as the need and preferences of the end-user.

During the drug development journey, pharmaceutical and biotechnology companies are increasingly speaking with the people

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they serve to ensure products are feasible, suitable, and tackle unmet needs. Consultation and patient engagement are equally important in the development of novel drug delivery systems.

One of the main benefits of PFS administration is the ability it gives patients to self-administer their medication at home, rather than traveling to see a healthcare provider. It means people must be able to use their devices safely and effectively in a non-medical setting.

Some patient groups, such as those with chronic conditions that affect dexterity for example, will have difficulty handling certain sizes or shapes of PFS. How the device is operated will also need to be tailored to the typical characteristics of the end-user.

It doesn't matter how ground-breaking and innovative a treatment is, it will make no impact on outcomes if the patient is unable or unwilling to use it.

Technical Challenges

PFS manufacturing presents several technical challenges which, again, must be considered on a product-by-product basis.

The high viscosity of biological products, which hampers clean dispensing, is probably the most debated of all these. Often, the medication solution will "stick" to the tip of the filling needle as it withdraws from the syringe, creating a trail. Not only does this result in expensive product waste, but it makes fill levels unreliable and can lead to safety-compromising dosing errors.

As with all things PFS, there is no one single solution. Reducing viscosity through heat is not usually an option, as biologic solution stability is often temperature dependent. Other approaches have used fill needle movement to break surface tension, but this can lead to a build-up of static charge when filling products more than 1,000 centipoise into polymer syringes.

AMRI's solution involves using a high-speed camera to film the needle motion, then aligning the retracting motion of the needles to the velocity of the pump motion dispensing of product. This process, which implements a short pause above the final liquid level, ensures the remaining product disconnects from the needle tip. It is effective, but still must be adapted to suit each individual medicine.

The choice between glass or plastic syringes has become a hot topic in recent years. Plastic is common in biologics where product viscosity requires a PFS that allows for a consistent gliding force during administration. However, it is not the right solution for every product and filling polymer products is not easy.

Improperly programmed machine movements or even minor equipment impairments can cause scratches, and while vacuum stoppering is commonly employed to overcome this, again, it does not suit every product. Customized processes, based on experience and expertise, are needed to ensure error-free filling and stoppering.

Ensuring the product is biocompatible with the drug delivery system, its components and materials is another safety-critical, not to mention regulatory mandated, process. The formulation of an injectable product will dictate a range of potential complex interactions with

the syringe components and packaging, all of which can have serious ramifications for the manufacturing process and the quality, efficacy, and safety of the end-product.

Factors such as the potential of polymer or glass to interact with the product, the drug's glass absorption parameters, pH changes, and potential extractables and leachables must all be assessed in the system design process. User-related factors, including the duration of contact between patient and PFS, and the nature of patient/delivery system interaction, will also influence PFS design and selection.

Navigating this complex tapestry of patient centricity and technical challenges requires in-depth understanding of the processes, techniques and products involved, and can only be approached on a case-by-case basis. At AMRI, an in-house analytical team serves as a valuable resource for our clients, providing expertise in extractables and leachables (E&Ls), container testing, heavy metal detection, and significantly aids in optimizing container closure design for a given product.

Partnering for Success

As outlined above, there is no one size fits all solution to matching products to an appropriate PFS delivery system. Each product is unique and requires bespoke mechanical, technical and compliance processes.

Overcoming the multitude of manufacturing and process challenges – and fulfilling the potential of this promising product/delivery system coupling – requires partnership.

With the average drug development pathway taking 10 years and costing $2.6B,[2] the biological medicines marketplace is fiercely competitive. There is little room for error, but by combining pharmaceutical and drug delivery expertise early on in the development process, partnerships can ensure new medicines are safe, effective, easy to use, tackle unmet patient need – and make it to market as quickly as possible.

Developer/CDMO partnerships offer an agile PFS approach that adapts to the needs to each product and its end-users. As individual patient groups will have varying requirements of the product itself,

and the packaging it is supplied in, the PFS design and development is usually most effective when it evolves in parallel to product design and development. In fact, many drug developers now work with their chosen PFS supplier as early as phase I.

Conclusion

The rise of biological medicines has played a major role in the growth of the PFS market. By necessitating a shift from oral to parenteral administration they have created a need for state-of-the-art, innovative delivery systems.

It is a trend that is set to continue as more biologics and biosimilars come online and as the promise of next generation gene and cell therapies come to fruition.

Dispensing highly viscous solutions, minimizing E&Ls and ensuring biocompatibility, all while developing delivery systems that suit individual patient groups, however, present unique manufacturing, compliance, filling and dispensing challenges.

By integrating expertise in areas such as drug processes, substance processes and analytics, CDMOs can streamline and optimize product development. Close working relationships, both within the organization and with partners and clients, can speed up problem solving and facilitate the creation of customized solutions.

Crucially, by working with PFS CDMOs, drug developers can benefit from their specialist expertise and expect shorter, smoother development pathways. Strong partnership working is the only way to ensure the innovative drug products of the future are delivered effectively, fulfil their potential and, ultimately, save lives.

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Outsourcing Solid Dose Manufacturing Trends

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Many recognized drug development challenges are impacting oral solid dose (OSD) manufacturing. Most notably, the ever more complex nature of new molecules that are frequently affected by difficulties related to their bioavailability, formulation, stability, manufacturability, and scalability. At a time when the pharmaceutical industry is already under pressure to reduce development timelines and the associated costs, many developers are choosing to unload some of the responsibility related to manufacturing OSDs by using the services of contract development and manufacturing organizations (CDMOs). These providers are not only bringing expertise to the table in the manufacturing of OSDs, but also offer the benefits of access to new technologies, formulation ideas and other processing innovations.

The Popularity of OSDs

Most medicines, from over-the-counter treatments to prescription drugs, are taken by mouth in the form of tablets or capsules. The convenience, flexibility, cost-effectiveness, and patient-friendly nature of OSDs, especially among the pediatric and geriatric populations, are just some of the reasons why these dosage forms have stood the test of time. As well as being relatively simple to package, OSD forms offer increased chemical and physical stability.[1]

They can also bring the opportunity to extend product lifecycles and leverage growth potential, with many developers employing various lifecycle management patent strategies, including the development of new drug formulations, such as extended, controlled, or rapid release formulations. These innovations are making it possible for OSDs to achieve enhanced bioavailability. At the same time, they are helping to improve the patient experience and, consequently, driving better compliance to dosing regimens.

The global OSD market is expected to grow from $493 billion in 2017 to $926 billion by the end of 2027. This translates to a CAGR of 6.5%.[1] More complex active pharmaceutical ingredients (APIs), different chemistries, smaller batches, advancing drug delivery technologies, as well as the introduction of continuous processing, are all adding to operational challenges for drug development teams. This is helping to fuel growth in the outsourcing market, with many developers now seeing CDMO partnerships as a vital component of their strategy.

OSD Outsourcing Market Drivers

Growth in the OSD outsourcing market may be attributed to three market drivers.

1. Customers with high volume products are increasingly looking for an improved set-up from a total cost of supply point of view. While in the past developers would typically only consider the total cost of contract manufacturing, they are now considering other factors, such as the location of manufacturing and the potential for this to cause issues and slow down the supply chain.
2. The requirement for more complex manufacturing processes is leaving many developers struggling to find the right technical set-up that is manageable from a cost standpoint. CDMOs that can offer a broad range of service and capabilities can help to simplify their supply chain.
3. More small/virtual pharmaceutical companies are developing drugs that they do not intend on manufacturing themselves. Instead preferring to choose to partner with CDMOs that can take responsibility for development from the start.

The Rewards of Outsourcing

While OSD forms may have a long history of successful use, their development and manufacture still presents a complex endeavor. Outsourcing can provide an answer to streamline development processes and achieve more flexible manufacturing, while reducing capital costs and gaining access to capacity and capabilities. It also opens the door to a broad pool of expertise, which can help mitigate risk for developers.

Working with a CDMO minimizes the need for in-house resources. Drug developers can take advantage of specialized processing technologies for the manufacture of controlled release products, as well as the capability to produce combination products with several APIs.

CDMO selection should be based on an organization's strong reputation in the industry. Developers ideally want to be looking at those providers that have a track-record for on-time delivery, as

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well as those that can deliver value for money through an attractive total cost of supply. The quality of relationships is also important in developing a collaborative partnership. Understanding how a CDMO will manage a pragmatic communication network and build regular dialogue with the development team should also form a key part of the selection process.

To ensure a smooth transition from development to commercialization, pharma companies will want to consider whether a CDMOs capabilities adequately match with their late stage requirements. It may be preferential to select a CDMO that can support the entire lifecycle and scale formulations from the laboratory to GMP clinical and commercial manufacturing. This can remove the risk, time and costs associated with technology transfer, as well as the requirement to manage multiple vendors. The robustness of manufacturing processes, capacity, trouble-shooting expertise, and access to global resources are also key attributes that should be considered a priority.

It is also important to understand a CDMO's ability to achieve fast turnaround times while maintaining high quality. A thorough interrogation of the internal systems, processes, and procedures that a CDMO has in place is needed to ensure that project milestones will be met.

A reliable CDMO should demonstrate a good understanding of a product. This will include how a drug substance behaves during processing, such as its solubility in solvents and buffer systems, compatibility with excipients, stability under various physiological conditions, solid-state characteristics, and physiochemical properties. This understanding will be crucial in ensuring the right delivery system is identified and the optimal drug formulation developed. With today's more complex compounds being prone to poor solubility, identifying the right formulation solutions which are faster to scale-up and offer a reduced likelihood of failure at the latter stages is vital in ensuring that a product reaches commercial manufacture.

Finally, complex projects will always present technical challenges and their own unique obstacles. Steps should be taken to identify a CDMO partner that can demonstrate experience of navigating difficult manufacturing projects. Being able to identify areas where problems are likely to arise will be essential to achieving success.

Conclusion

The dominance of OSD products in the pharmaceutical industry shows no signs of slowing down, with developers continuing to invest significant R&D expenditure toward more effective and patient-friendly solid forms. As increasingly complex molecules continue to drive demand for more diverse technical requirements and supply chain needs, outsourcing is becoming a crucial component in ensuring these products reach commercial manufacture in the most efficient way possible.

CDMOs have become a vital part of the OSD drug development and manufacturing process with most small and medium-sized enterprises (SMEs) and an increasing number of big pharma relying on their services. Providers that have the ability to work on a project from early development through to commercial manufacturing are able to gain a solid understanding of the OSD product being developed and are better equipped to handle any challenges that may arise during a project. As a result, an end-to-end service offering delivers an efficient manufacturing process and can improve supply chain efficiency.

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Erik Haeffler is the Vice President of Manufacturing Services and the Head of Sustainability at Recipharm. He is responsible for the Group's sustainability work, as well as its focus on operational and commercial excellence. As part of his role, Erik is continuously developing a model for working with multi-site projects and is accountable for operations development across the company, including elements such as project management resources, corporate IS and project/product sourcing decisions.

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Overcoming Challenges with Amorphous Materials during Micronization

Fergus Manford, Matthew Green and David Thomas

Vectura

The mechanical process of reducing the size of a material using high-energy systems is known as micronization. There are two major benefits from reducing the size of the particle in a pharmaceutical product: firstly, broader ranges of target sites are available; and secondly, smaller particle size results in an increase in the surface area and this facilitates improved clinical efficacy. The resultant particles are physically unstable with regions of induced disorder, otherwise known as amorphous material.

The process of reducing the size of convergent particles with two or more opposing currents was invented in 1881 when Frederic A. Luckenbach and John Wolfenden received their patent for an opposed fluid energy mill,[1] but it was another 65 years before the first commercially-practical jet mills were introduced by The Jet Pulverizer Company. Prior to Luckenbach and Wolfenden's invention, substances had been pulverised by grinding, stamping, or using powerful jets of air to project them against a metallic disk. However, there were disadvantages to this approach, such as powder contamination and mechanical wear and tear.

Modern micronization equipment still bears some resemblance to the equipment used back in the late 19th century. A jet mill, also known as a fluid energy mill, uses pressurized gas to produce high-energy particle-particle collisions within the jet mill grinding chamber. These high-energy collisions result in micrometer-sized particles or agglomerates of nanometer-sized single crystal primary particles.[2] In some cases, they can also produce composite particles, which is where a host particle is coated with a second substance.

There are alternatives for producing small particles, such as spray drying, co-precipitation/crystal precipitation and particle homogenization, but none of these methods offer the same scalability as a jet mill. Furthermore, there are no moving parts within a jet mill and little heat associated with the milling process due to cooling effect of the jets, which is important in maintaining the stability of the active pharmaceutical ingredients (API).

Technical Challenges

The micronization of APIs presents a few technical challenges, in particular the inadvertent formation of amorphous regions of material at the site of particle-particle collisions.[3] These regions are non-crystalline and lack the continuous structural order that is characteristic of a crystal. This presents a number of problems for formulators, and is especially problematic for inhaled API particles because the different properties found in amorphous regions can elicit a change in the aerosol deposition profile on storage. Amorphous regions often require additional processing to obtain a stable product prior to formulation. In extreme instances this can result in a micronized product that cannot be formulated using conventional manufacturing processes.

The extent to which the API forms amorphous regions depends on the material and the energy imparted during the micronization. Jet mills impart large amounts of energy to the milled material, leading to the production of proportionally more amorphous material. If the amorphous particles can be controlled and remain amorphous, this can be considered a controlled state, but in reality, this is very difficult to achieve. Amorphous materials are unstable and will attempt to revert to the more stable crystalline state. Water, in the form of moisture in the air, often facilitates this reversion.

Where amorphous surfaces are in contact with each other, the process of amorphous to crystalline reversion is particularly problematic. The abutting amorphous regions undergo simultaneous amorphous to crystalline reversion but this reversion bleeds into the neighboring particle causing the two particles to adhere to each other once they are crystalline. Since powders are rarely diffusely spread to the extent that neighboring particles are not in contact, when amorphous material is spread across an entire powder bed large agglomerates form in an unpredictable manner. Furthermore, upon reverting to the crystalline state, water is given up by the amorphous material thereby further facilitating this reversion.

Advanced Jet Milling

To avoid the formation of amorphous material, jet mill operators have tried to maximize the amount of water vapor in pressurized gas lines to achieve milling gas humidity in the region of 30 to 70% relative humidity (RH)[4] while avoiding the production of a liquid condensate in the grinding chamber.[5,6] These methods, however, require bespoke apparatus or costly modifications to supplement pressurized gas lines with moisture.

A recently developed technique that increases the capabilities of jet milling, introduces a liquid aerosol into the jet mill's grinding chamber, thereby enabling the manufacture of a stable amorphous-free product without the need for additional time-consuming conditioning processes or costly manufacturing apparatus.

Introducing a liquid aerosol directly into the grinding chamber at the point of micronization avoids contaminating the pressurized gas lines leading to the jet mill grinding chamber. The liquid aerosol can be introduced under ambient temperature conditions that are less likely to denature delicate material, such as biologics. The use of a liquid aerosol also avoids the need to either heat the milling gas, or to modify or contaminate the pressurized gas feed lines. If required, the liquid aerosol can include one of, or a mixture of a pharmaceutically-active material, an additive and an excipient depending on the formulator's requirements. This now expands the capability to manufacture a greater range of morphologically different products in a jet mill including, for example, API combinations in a single particle.

Case Study: Jet Milling with Liquid Aerosol

A study was carried out to demonstrate that adequate moisture levels in the presence of high velocity collisions assist with the reversion of the surface amorphous regions back to crystalline material, thereby obtaining a thermodynamically stable particulate product.

Glycopyrrolate (a quaternary ammonium compound) was chosen as a model API because it readily demonstrates physical instability when micronized under dry conditions, and has a known susceptibility to produce amorphous material during comminution.[7]

This instability is demonstrated when the amorphous regions between neighboring particles revert to their crystalline form, resulting in inter-particle bridging, rendering the material unsuitable for use in an inhalation product.

A controllable ultrasonic water nebulizer was positioned across the venturi of a spiral jet mill to introduce liquid aerosol at the site of comminution. The output gas humidity was measured using a portable hygrometer

inserted into the exit port of the jet mill and recorded throughout each processing run.

As a control, glycopyrrolate was micronized using dry micronization conditions (formulation A), whereas the test material was micronized in the presence of liquid aerosol (formulation B). The micronization was performed using compressed air with an inlet pressure of 5 Bar, a grinding pressure of 3 Bar and an average feed rate of 2 g/min delivered via a vibratory feeder.

The particle size distributions were determined by both wet and dry laser diffraction analysis methods and the amorphous content was assessed by dynamic vapor sorption (DVS), immediately following the micronization step.

Dry analysis involved using a laser diffraction particle size analyzer, equipped with the dry dispersion method at 4 Bar. Wet analysis used the laser diffraction particle size analyzer equipped with the wet dispersion unit, filled with iso-octane (2,2,4-trimethylpentane). This pre-dispersion was sonicated for three minutes using a sonic probe at 50% intensity. The optical properties for both methods used a refractive index of 1.52 and an absorption value of 1.0.

DVS was carried out using an automated multi-vapor gravimetric sorption analyzer. The humidity was increased from 0–90% RH then returned to 0%, both in steps of 10% RH. The DVS methodology required a mass change of 0.001% dm/dt before moving on to the next step. A time-out limitation was imposed in the event the threshold was not met within the predetermined period of six hours. In addition, samples were stored for 24 hours and then photographed to illustrate the re-crystallisation.

The effects of uncontrolled re-crystallization are illustrated in Figure 1. Initially, both samples contained a level bed of micronized glycopyrrolate (indicated by black line on each scintillation vial), but

Figure 1. Glycopyrrolate stored for 24 hrs; A) dry micronization, B) micronization in the presence of liquid aerosol.

Figure 2. Glycopyrrolate micronized using dry jet milling conditions (2.8 – 3.5% RH)

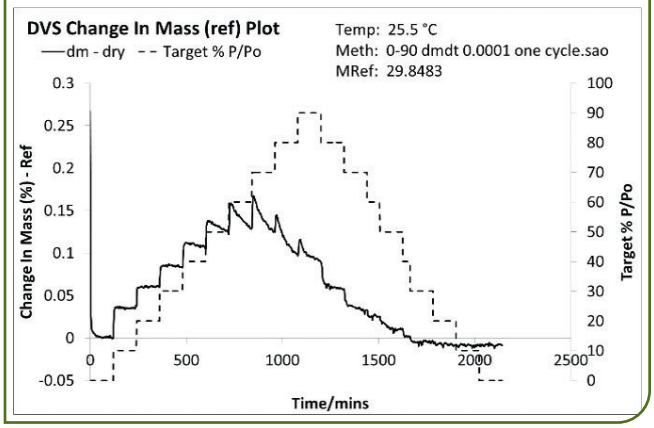

Figure 3. Glycopyrrolate micronized using dry jet milling conditions (31.6 – 36.2% RH)

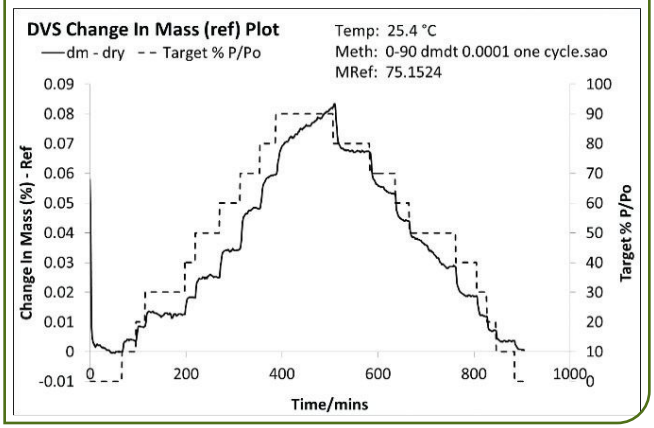

Table 1. Particle size analysis of glycopyrrolate micronized under dry conditions or in the presence of liquid aerosol

Glycopyrrolate micronization	Particle size (wet n=6, dry n=3)	d_{10}	d_{50}	d_{90}	In-process humidity range (%RH)
Raw Material	wet	20.6	148.7	409.7	n/a
Formulation A	wet	0.8	2.1	3.9	2.8 - 3.5
	dry	1.1	250	1340	
Formulation B	wet	1.4	4.1	9.1	31.6 - 36.2
	dry	0.4	2.7	9.2	

over 24 hours, Formulation A contracted in both the horizontal and vertical planes resulting in a frustoconical cone and turned into a solid mass. However, Formulation B remained as discrete particles with no change in bulk volume.

The particle size analysis results (see Table 1) demonstrate the change in particle size distribution resulting from the re-crystallization. There is a clear increase in measured particle size, which is believed to be due to the agglomeration of primary particles.

The wet laser diffraction analysis method employed a sonication process that is capable of breaking the agglomerates into their primary particles; the dry laser diffraction analysis method did not use a sonication process but instead used a 4 Bar dispersion pressure which is incapable of breaking these agglomerates.

Under ambient conditions, this agglomeration started immediately following micronization. In contrast, when the liquid aerosol was used in the process, the size of the resultant particles remained stable, confirming the visual observation shown in Figure 1.

This stability is believed to result because particle micronization in the presence of liquid aerosol creates an environment for the amorphous material to quickly convert back to the crystallized form before these particles have an opportunity to agglomerate.

The DVS traces (Figures 2 and 3) show the presence of amorphous material in the two formulations.

Conclusion

Adequate moisture levels in the presence of high velocity collisions assist with the reversion of the surface amorphous regions back to crystalline material, thereby obtaining a thermodynamically stable particulate product. Contrary to conventional thinking, the results of this study demonstrate that when liquid aerosol is introduced into the grinding chamber of a jet mill it does not create a slurry. Instead, the liquid aerosol confers important benefits without the need for time-consuming conditioning processes or costly manufacturing apparatus.

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Bioprocessing 4.0 – Where Are We with Smart Manufacturing in 2020?

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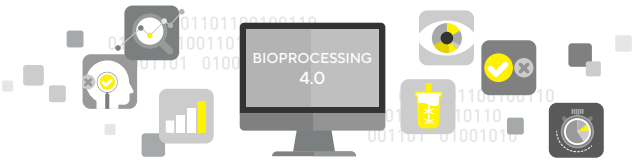
Introduction

The term Bioprocessing 4.0 has been tossed around since 2018 and is derived from Industry 4.0, a national strategic initiative from the German government launched in 2010 with the aim of driving manufacturing forward by increasing digitization and the interconnection of products, supply chains and business models.[1] Bioprocessing (or Bioprocess) 4.0 today is defined as a totally end-to-end connected bioprocess, where all systems and equipment in the process are connected digitally, forming the Industrial Internet of Things (IIoT) to run, control and even improve the process via feedback loops and artificial intelligence (AI) or machine learning. IIoT is redefining automation architecture and simplifying the automation pyramid by compressing many of the lower layers and also upper layers. Sensors, instruments, and other devices are interconnected directly to the cloud for data collection and analysis, as well as optimized process controls. Due to the need for real-time control capabilities of bioprocess workflows, Bioprocessing 4.0 relies heavily on integrated data management and analytics, modelling and automation, as well as cloud and edge-based computing for the vast amounts of data it produces.

The biopharmaceutical industry has lagged behind other industries, such as oil and gas, where they have been using integrated processing since 1995, as well as finance and the semi-conductor sectors, which have been using end-to-end digitization since 2000. One reason for the biopharmaceutical industry being behind is that



unlike many other industrial processes, bioprocessing is not binary and generally involves complex living cells where variability is high making measurement and predictions of bioprocess performance challenging. The industry is also heavily regulated, with special constraints around contamination and safety, where changes to a Good Manufacturing Process Compliant (cGMP) locked down process are viewed by bioprocess scientists as tricky to implement. Another reason is that process automation capable of culturing cells and purifying biologics in bioprocessing was in its infancy in 2000, as were scale-down models for predicting process performance and Process Analytical Technology (PAT) tools for real-time bioprocess monitoring.

Some might say that Bioprocessing 4.0 really began to take off after 2004, with the publication of the FDA's guidance on PAT and (Quality by Design) QbD, which aimed to reduce process variability and thereby improve quality, safety and/or efficiency in drug manufacturing.[2] The idea has been driven forward by a number of industry bodies including the Biophorum (BPOG)

with its Biomanufacturing Technology Roadmap in 2017.[3] This was followed by its plug and play initiative in 2018[4] and The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) with its ICH Q12 guidelines.[5] Each of these initiatives and guidelines has helped galvanize forward-thinking biopharmaceutical companies and life science equipment suppliers into action on standardization and integration of bioprocess automation.

Who's Embracing It?

Biopharmaceutical manufacturers are being driven to adopt Bioprocessing 4.0 by market pressures to produce biologics in a shorter timeframe without compromising product quality and safety. The SARS-COV-2 pandemic has magnified the need to do this because of the time-critical need to produce vaccines to prevent and therapies to treat this novel Coronavirus.

The ideal Bioprocessing 4.0 manufacturing facility for rapid, flexible production would include fully automated upstream single-use (SU) bioreactors designed for intensified processing using high cell density fed-batch culture or perfusion culture. The bioreactors would have associated SU in-line sensors, providing real-time information to determine or estimate Critical Quality Attributes (CQAs), such that scientists could gather data for release decisions while the process is running. These facilities would also have 'digital twins' of bioprocess equipment, such as bioreactors and chromatography columns, which are *in silico* simulations of the process, that can be used for improved process control or run simulations in place of physical experiments when needed. Using this type of Bioprocessing 4.0 set-up would mean weeks could be shaved off process runs because there would be less waiting for off-line data testing and feedback, we could run virtual process testing, and time for cleaning and cleaning validation of equipment would be virtually eliminated.

Companies such as Biogen are actively working towards Bioprocessing 4.0 with studies by Ahmed et al in 2019 where they have constructed a hybrid model or 'digital twin' of their cell culture process, which includes cell growth, glucose consumption, lactate, glutamine, glutamate and ammonia production, as well as titer data to simulate a high titer monoclonal antibody (mAb) production bioreactor.[6]

Sanofi has also embraced Bioprocessing 4.0 in its new biomanufacturing facility in Framingham, Massachusetts. The plant, which opened in 2019, is highly digitized with closed loop controls for intensified, continuous biologic production using automated data capture from a range of sensors. The cloud-based data can be accessed from anywhere in the world in real-time to assess bioprocess runs and make process changes if necessary. Sanofi has also generated 'digital twins' of its production bioreactors, so that bioprocess scientists can simulate manufacturing process changes.[7]

Bioprocessing 4.0 is not just about controlling process runs, and Amgen has recognized that actively managing the supply chain is an important piece in the puzzle and has set up a Supplier Relationship Excellence (SRE) program to create a feedback loop where electronic data is exchanged with raw material suppliers. The program aims to understand operational performance by developing data exchange standards, using predictive models to anticipate supply issues or identify any improvements[8] and thereby ensure biologics' quality is continuously achieved without any issues.

Game Changing Technology

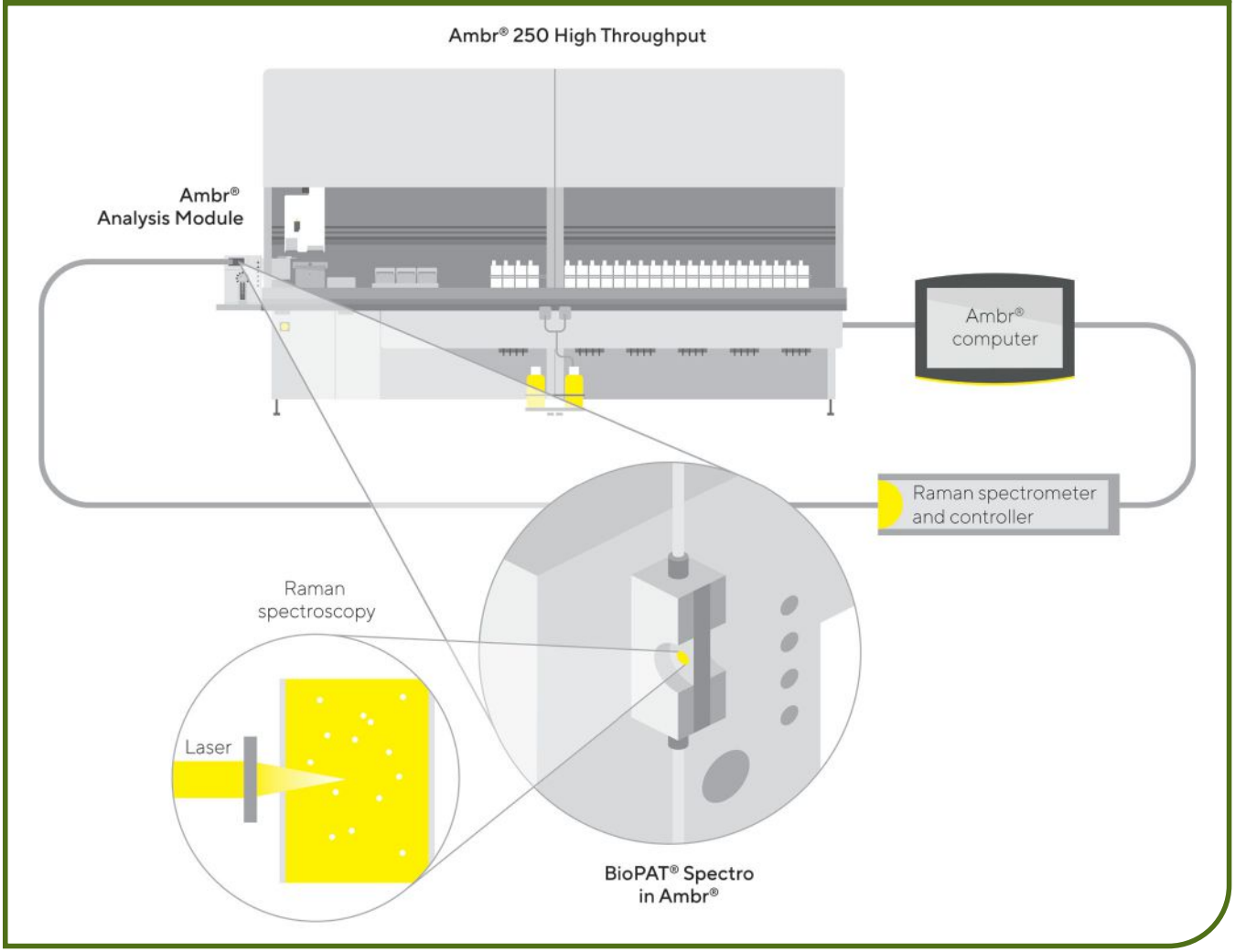
In the past decade, a technology platform that has been helping to move the biopharmaceutical industry closer to Bioprocessing 4.0 in the upstream is the high-throughput automated scale-down bioreactor mimic. These mini bioreactors have been shown to provide robust estimates of process performance and product quality from bench to pilot scale in studies by Lewis et al at AstraZeneca[9] and Hsu et al at Genentech.[10] They have also recently been used in 2019 as a qualified scale down model for process characterization by Manahan et al at Merck in large-scale commercial bioreactors (>10,000 L).[11] Using mini bioreactor technology with PAT tools that can be transferred between SU bioreactor scales offers a simpler method of integrating and digitizing an end-to-end upstream process.

Aligned with mini bioreactor technology, spectroscopy is an analytical technique that is helping move the upstream Bioprocessing 4.0 dial. Spectroscopy techniques such as Raman, Fourier-transform infrared (FTIR) and Near-infrared (NIR) are beginning to replace off-line HPLC and autosamplers because these off-line measurement methods are time consuming and cannot provide in-line feedback loops for real-time monitoring and control as Raman spectroscopy, for example, can. The use of spectroscopy techniques looks set to increase in the next decade as they are tackling some of the pain points of measuring cell culture and monitoring CQAs of biologics.

Currently in-line Raman spectroscopy is being used in pilot and manufacturing scale cell culture. But there are studies that indicate this technique has the potential to be used as an automated on-line method to measure multiple analytes simultaneously in mini bioreactors[12] (Figure 1). Biopharmaceutical companies such as

Digital twins of bioprocessing equipment are often used in Bioprocessing 4.0 facilities.

Figure 1. Mini bioreactor technology with an integrated Raman spectroscopy platform

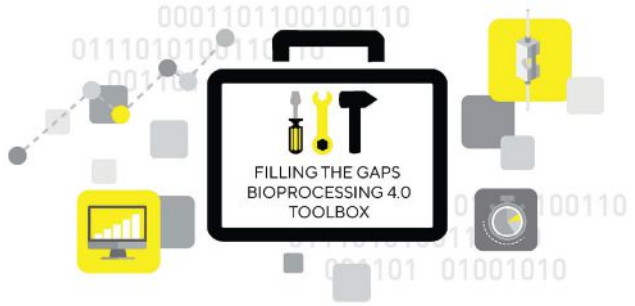


GlaxoSmithKline are working with integrated Raman spectroscopy from mini bioreactors through to manufacturing vessels to rapidly and more easily build models that can control their bioreactors.[13] Having this integrated real-time PAT technology from process development though to manufacturing scale will help to build Bioprocessing 4.0 upstream cell culture processes in many biopharmaceutical companies in future.

Where are the Gaps?

In general, upstream is further down the Bioprocessing 4.0 road in terms of connectedness and digitization than downstream. This is because downstream processing relies on more traditional, less automated equipment and techniques with fewer in-line sensors and it is often difficult to connect all the parts of the process, which means there is less opportunity to collect meaningful data and control processes, leading to high variability in downstream bioprocessing. What is required now is the capability to connect downstream equipment together more easily, (the increasing use of ballroom style skids is helping here), as well as the use of more PAT sensors to collect data on process variables. Also design of Experiments (DoE) studies using scale down high throughput columns and filters and multivariate data analysis (MVDA) of the results are needed to predict the effects chromatography resins and filter pressures, for example have on processes and CQAs.

With the level of integrated SU technology and in-line sensors available in the upstream, it should be easier for many biopharmaceutical companies and CDMOs to be implementing Bioprocessing 4.0 here. Yet this is still not the case. One of the main reasons many companies are not implementing Bioprocessing 4.0 in the upstream or downstream is bandwidth and budget constraints. Many smaller biopharmaceutical companies and CDMOs simply do not have the money or the staff available with the right skill set that can spend



time making sure their processes and analytics are fully integrated. This is an area where equipment and software suppliers can assist, and they should try to ensure that their products are as ready to use for seamless integration and digitization in manufacturing facilities as possible.

Another reason why many biopharmaceutical companies are wary of Bioprocessing 4.0 is a lack of regulatory guidance. Although, the FDA has issued information on implementing ICH Q8, Q9, Q10,[14] which is beginning to put boundaries around processes and product quality, guidelines around some automation and sensor technologies are missing. For example, Raman spectroscopy sensors that measure multiple analytes in cell culture are not fully covered. Additionally, there is limited guidance on how to validate chemometric models generated from Raman spectroscopy with MVDA for use in GMP facilities. With the increase in use of continuous instead of fed-batch culture in the upstream, there is a much greater need to validate PAT methods such as Raman spectroscopy as these can be used for in-line monitoring and feedback control of processes that could potentially have much longer run times and where the definition of a "batch" is unclear. The FDA has given some good strategic guidance on spectroscopy; however, the biopharma industry needs more prescriptive guidance, which is likely to come when the ICH Q2/Q14 guidance (currently in draft) is published and should improve communications between regulators and the industry.[15]

Finally, there is a lack of skilled technical staff to run Bioprocessing 4.0 type facilities as many educational institutes are not providing the right kind of training with very few courses on advanced process control currently being offered. This gap could be plugged by equipment suppliers, if they can hire enough IT experts with a diverse skill set to develop software and automation that can be used intuitively with minimal training by operators on the shop floor. However, this means suppliers need to invest time in understanding the bioprocess workflow and how the different personas of people working along it interact with the equipment from a user experience point of view.

Conclusion

Despite Bioprocessing 4.0 with its integration and digitization promising better process consistency to improve quality and safety in biologics manufacturing, only a handful of biopharmaceutical companies are currently embracing this initiative. However, by leveraging technology advances including mini bioreactors for process development, SU scalable bioreactors, PAT tools for automated in/on-line spectroscopy and MVDA, Bioprocessing 4.0 in the upstream at least is becoming more widely achievable. In the downstream however there is still a way to go with automation, PAT tools and data analysis. If clear regulatory guidelines, improved access to the right type of training for scientists and delivery by suppliers of equipment and software that harmonizes with a plant's digital connectedness can be achieved, then a tipping point will occur, so that by 2030 Bioprocessing 4.0 manufacturing facilities, which can be operated from anywhere in the world, will become commonplace across the biopharmaceutical industry.

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Building Future-Proof Supply Chains with Graph Technology

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The life science manufacturing and supply sector has seen unprecedented disruption. Many pharmaceutical manufacturers have had to pivot their product lines within weeks and global supply lines have struggled to fulfill changing demands. Post pandemic, life sciences companies will be taking a long, hard look at how they can build more robust supply chains. Graph database technology that records and handles complex data interdependencies is increasingly critical.

Massive variations in supply and demand have stressed supply chains to a breaking point. Pharmaceutical companies have had to switch their product lines almost overnight to meet demand for completely new medicinal products and devices to treat patients with coronavirus. Pharmaceutical manufacturers and supply chains have had to act quickly to respond to these changes.

While the global effort to pivot product manufacture and supply chains has been unprecedented, it highlights the need for greater efficiencies in processes across the board. It has become clear that manufacturers, distributors and supply chain companies need a more agile way of dealing with the vast amount of intertwined data and regulations involved with delivering items around the world. Life sciences organizations need a highly scalable way to manage the huge volumes of serial numbers, supplier and facility details, certifications, documents and detailed questionnaires they will need to track to get on top of the crisis.

Real-Time Insights for Smart Decision-Making

There is a pressing need to build stronger, scalable and more flexible supply chains. To achieve this, pharmaceutical companies will need a better understanding of the data flowing in and out of their supply chains, so they can gain real-time insights for smart decision-making. At the same time, brands may need to win back consumer and customer confidence, and in some cases, loyalty. All of this needs to happen as quickly as possible – while ensuring products meet international standards and regulations without compromising their standards for sustainability and social responsibility.

In an ideal world, supply chains would be a linear chain of single suppliers, logistics and distribution. Unfortunately, real life is much more complicated. Many pharma companies still have their data stored in silos, meaning they only have a partial view of what is going on in their supply chains. And even if the data is stored in a single relational database, understanding the connections between products on a production line, or substances waiting to be shipped, is extremely challenging. Packaging and labelling product lines which are rapidly changing is a major challenge.

As data and processes become increasingly interdependent, there is greater potential to gain data-driven insights – and a commensurate increase in complexity. Relational database technology, which stores data in rows and columns, is poorly equipped for identifying relationships within datasets, but these connections are imperative for identifying a product's whereabouts as well as monitoring, analyzing and visualizing the supply chain and supporting logistics changes. These connections also need to be easy to search, and performant enough to provide timely insights even for the largest, most complex supply chain.

Making traditional databases perform multidimensional tasks in real time is also very difficult, with performance degradation as the size of the total dataset grows. Companies need a scalable, agile way of managing thousands of different product lines, produced across multiple sites, which are sold into hundreds of diverse markets. Using SQL-based database technology, simple and fast navigation through all the data in order to recognize how a production line or particular pallets and their contents are connected is next to impossible.

Meeting Regulatory Challenges

With regulations on the horizon that mandate more detailed serialization data interchange along the pharmaceutical supply chain, many companies are working hard on building interoperable systems. But traditional databases are struggling to support interoperability ambitions.

The ripple effects of the pandemic are putting companies at risk of delivering products that are below par or don't meet regulations. Sub-

standard components may be hastily ushered into the supply chain without being scrutinized and could place manufacturers' entire operations in a perilous position. Packaging may be sub-optimal due to supply issues or changes in the products being shipped. This poses additional risk in closely-regulated industries such as pharmaceuticals or medical device makers, where suppliers must be able to identify and locate an individual item or batch at any given time.

Until it was overtaken by the COVID-19 response, environmental sustainability was perhaps one of the most pressing issues in the pharmaceutical manufacturing sector. Graph technology enables companies to gain a clear view of complex data interdependencies that highlight error, waste and duplication in processes, allowing companies to optimize processes for both speed to market and waste reduction. When the new normal emerges, environmental and sustainability concerns and the need to review and redesign supply chains to be more robust will be top of mind.

Speeding Query Response

With greater visibility into supply chains, it becomes a lot easier to drill down to gain an accurate, trackable picture of products and their whereabouts. Graph database technology can record and handle complex data interdependencies. Using graph tech, manufacturers can typically demonstrate 100 times faster query response speeds than those enabled by SQL RDBMS software. This agile response is critical during the present crisis and will be crucial going forward in a highly digitized, increasingly competitive world.

Performance is maintained, even with vast quantities of data. Scan the code on a particular pallet and it can display not only all of its contents but also the context, such as which ports it was shipped through, when it was manufactured, and even the relationships between manufacturers.

Rather than using relational tables, graphs use structures that are better at analyzing interconnections in data. Graph data models are flexible and do not need to be hardcoded, making a graph database practically impossible to beat when it comes to analyzing the relationships between a large number of data points. Such a connected relationship-centric approach allows businesses to better manage, read and visualize the data in lengthy and complex supply chains.

Tackling the Reality of Complex, Interconnected Supply Chains

Graph technology goes far beyond simply digitizing supply chains. The technology can be used now to tackle the current reality of complex, interconnected supply chains, delivering the transparency and traceability required to enable manufacturers to rapidly identify risk and respond to disruption.

While no-one could have predicted the scale and the speed at which the pandemic unfolded, could we have been better prepared? It's a problem summed up by The World Economic Forum, which warns that, "Governments, businesses and individual consumers suddenly struggled to procure basic products and materials, and were forced to confront the fragility of the modern supply chain. The urgent need to design smarter, stronger and more diverse supply chains has been one of the main lessons of this crisis."

It is essential to start working now. We need to put the right technology in place to provide deeper insights into existing data to give companies the agility and flexibility needed to survive and thrive. Graph database technology could be a real enabler here, providing a collaborative platform where gargantuan amounts of connected data can be handled at scale, to uncover business critical information.

Companies that have 360-degree visibility of their supply chains and supplier ecosystem are well equipped to know how production will be impacted. They will quickly realize that they need to look for alternative sources if there is a shortage of components, for example, or if ports are locked down. Those who are not prepared for this, or indeed the next black swan event, will find it almost impossible to mitigate supply shock and manage associated demand volatility.

Gain Actionable Insight

Delay and disruption have concentrated minds on building more resilient, adaptable supply chains. This is likely to drive the adoption of automation and data sharing along the supply chain, and further integration between manufacturing and logistics systems. Data insight will also be key. Automation and the Industrial Internet of Things (IIOT) will also create even more data sources.

It is no longer an option to approach data analytics using traditional relational databases. Using graph database technology, companies can uncover relationships between data that they would not have found using traditional approaches. The technology supports manufacturers as they derive the maximum value from supply chain data. This will be increasingly important in the new normal, where pandemic response will become part of every business' resilience plan.

Graph technology can provide actionable insight right now. It provides granular insight into manufacturing and supply chain data interdependencies, throwing supply issues into sharp relief. This in turn enables life science companies to drive efficiencies and accelerate the pace of change as they prepare to meet the challenge of an increasingly uncertain future. After all, if a supply chain is only as strong as its weakest link, we should be using graph databases to best understand the interconnections involved in bringing products to market.

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What if Jumping Through Regulatory Hoops Had an Upside?

Xavier Duburcq, CEO

ProductLife Group

Life sciences regulators exist to hold companies to account and keep customers safe, by enforcing certain standards and ensuring that manufacturers adhere to them over time (and can demonstrate, on demand, that they have done so). In the pharmaceutical sector, manufacturers have become accustomed to the significant and increasing 'burden' of regulatory compliance: of having to update their processes, systems and skills to accommodate the latest reporting requirements.

But maintaining compliance can be relentless. Each time companies think they have got on top of everything, one set of specifications is updated or a new wave of change comes along. It can be demoralizing, and draining – from a time and resource perspective. A better way to drive value from an investment in compliance is to look for a wider range of wins. Traditionally, companies would have approached regulatory requirements as a necessary evil, something to satisfy the authorities and minimize business risk. Beyond this, organizations have not typically looked for strategic benefits.

A Data-Driven Future: Reap the Benefits Many Times Over

In today's digital new world, there is a chance to treat compliance very differently. That's as companies move away from processes built around manually filling in paper or PDF documents for each unique regulatory reporting requirement, toward building rich, dynamic databases whose contents can be re-purposed many times over. A definitive central resource where all of the required information (and more besides) can be collated, checked, refined and updated – so that anything else that happens thereafter with that information is, by default, correct and compliant.

The pharmaceutical sector has tended to be slow to adapt to the benefits of this approach - because of the legacy data, systems and processes companies have had to unravel first. But unless they strive to do things fundamentally differently, they will be increasingly at a disadvantage.

Basing compliance activity on structured, ready-to-go data, in a consistent format, means the latest, correct information can be called up and prepared at speed using the latest digital tools to ensure efficient data exchanges with authorities, with full details/a clear line of sight across every product right along its lifecycle – for reliability traceability and protected data access.

By harnessing these characteristics, pharma companies can start to think beyond the immediate goal of compliance for its own sake, and toward the wider benefits that come with being able to quickly access great detail about products - including their application, use, and efficacy in the real world.

The Drive to Be Better: Demonstrating Core Values

Traditionally, audits, inspections, complaints handling, and pharmacovigilance, have put the spotlight on *non-compliance*. It is why, in the US, we see lawyers and other professionals with roles dedicated to damage limitation and crisis management.

But what if positive action and pre-emptive compliance were made business differentiators? If they became a signal to the market, and to customers/patients, that a company has an enriched sense of public duty, of 'wanting to do the right thing'? Amid the continued COVID disruption, and more recently the Black Lives Matter movement, there is an expectation that businesses review their culture, policies, and practices. Markets and customers have heightened sensitivity to whether companies are 'walking the talk', or whether everything they do is secondary to making a profit.

In life sciences CMC and, more recently, safety disciplines, new concepts have been developed by adopting a proactive rather than a defensive approach to compliance. The 'Quality by Design' initiative in CMC makes it possible to incorporate potential non-compliance risk in the development phase of the manufacturing process, for instance. The idea is to establish methods to increase robustness, minimizing

post-market manufacturing inspection impacts. And, by extension, improve the patient experience by bringing better products to market, faster.

The premise of proactive safety planning is similar – eliminating more risk at the outset, simultaneously hitting two targets: a higher/faster market success rate; and becoming a more trusted brand/supplier. Here, risk management plans involve anticipating and paying close attention to an initial holistic review of all aspects (both positive and negative) of a product from its earliest development stages, allowed to anticipate and mitigate the safety profile of each drug.

Boosting Public Perception: Raising Safety Standards

In a world where more and more detail is captured about products, and shared with agencies right across their lifecycle – in some cases even made accessible to the public through digital channels - anticipating non-compliance becomes strategically important for a whole range of reasons. Companies don't just want to avoid fines; they want to improve their safety records and show the public where their priorities really lie.

Companies can still look for cost efficiencies in all of this. Rather than lament next waves of regulatory demands, smart companies will look out for them – and be ready.

This means maintaining active 'compliance intelligence' - proactively identifying and anticipating trends in emerging rules, laws, or good practices. Regulation rarely comes out of nowhere. First, positioning papers are composed, shared and developed. Then, guidelines and staged implementations follow, with time allowed for transition. Where once the tendency might have been to 'wait and see', in case of delays or changes to requirements, companies are realizing increasingly that deferring action can put them on the back foot and render them less able to capitalize on adjacent opportunities for the business, and for customers/patients.

With new waves of regulatory advancement never far away, there will never be a better to time to transform compliance measures.

Forewarned is Forearmed

We generally advise the relevant team within the company - or a suitable partner - to conduct a risk assessment within the context of the organization's current business model, highlighting points to anticipate as new requirements appear on the horizon.

Once official requirements are published, the next task is to perform a gap analysis identifying all the potential implications arising. These might range from a simple but time-consuming review of a number of inter-related documents and data that will be involved/affected, to potential additional technical and scientific work (e.g. to replace a banned ingredient/questionable material by another) - and then gain approval from the authorities for any changes made.

Where a company has adopted a proactive approach to compliance - better still harnessed compliance as a lever to optimize the way it develops and manages its products - then the really smart thing to do is capture the lessons learned, perform a risk assessment and engage in process changes through a controlled transformation process.

By elevating compliance to something higher, more proactive and a powerful contributor to business success and patient outcomes, companies might also consider spinning off the whole activity. This could involve appointing a dedicated team (usually associated with a risk management department), or even relying on a service partner to outsource it. Certainly, continuing to react to each new requirement as it comes along - with reluctance and resentment at the resources it will consume – is no longer sustainable in 2020.

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Preclinical Testing: Advice for the Smaller Drug Developer

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Drug development companies come in all sizes and compositions, and it is safe to assume that no matter the makeup – they are all feeling the effects of the global pandemic, both professionally and personally, in their communities. Smaller pharmaceutical and biotechnology companies likely feel these implications more acutely, especially for projects that begin with a few scientists and a molecular breakthrough and need to be taken to the next step to access this critical market. From securing funds, limited internal capacity and other challenges that come with being smaller, these companies also face added obstacles throughout the drug development process.

Getting a compound to Investigational New Drug (IND)-enabling studies and the completion of the overall drug development application represents a major milestone for any company and project team. However, the preclinical testing process can be challenging for those with lean team structures or narrow expertise, and it represents a paradigm shift from discovery research to regulatory toxicology. In this case, small drug development companies can use these specific strategies and tactics to help them plan effectively and efficiently.

Start with the End Goal in Mind

Successful drug development can often be attributed to teams that plan realistically and proactively for proper preclinical studies and the completion of the IND application. These teams start with the ideal filing date and work backward, asking themselves if the timing is practical and taking into account the realistic capabilities of their staff and other resources.

Smaller companies should keep the end goal top of mind and account for the various pieces of the puzzle. Fundamental aspects of successful teams include:

- Understanding of the current market conditions
- Assessed demand for new drugs and novel approaches
- Current intelligence and available therapies in the therapeutic area of interest
- Realistic budgeting
- Thorough research and development
- *In vitro* molecular characterizations
- Highly functional modes of communication with outsourcing providers

With a firm grasp on these elements and a focus on the end goal, making sufficient headway to meet key benchmarks for time, money and resource allocation becomes achieved more easily. Productive companies are continually asking themselves important questions such as, "Have we met financial milestones?" Or, "Have we assembled a dynamic, effective and productive working group?" Mindset is everything, and moving a compound forward from kickoff to market is an extensive and dynamic process.

Drug Development Paralysis

Every drug development company knows the value of communication, but an easily forgotten factor is a definition of roles and responsibilities in each development area. Remaining open and adaptable to whatever the process throws at them is an important quality for smaller drug development companies. Rather than always wondering if there is a piece to the puzzle that's missing, assign roles and clarify ownership to mitigate team stasis. Dropping the ball on working with outside partners, logistical needs and other major areas can be detrimental to a project, so having leaders across all sectors maintains clear and measurable goals, unambiguous responsibilities and relevant communications critical to success.

Embracing Adversity

When things go wrong, it's easy to panic. For example, if preclinical testing reveals adverse toxicology findings in a compound, it can be interpreted as a failure in a variety of ways, and in reality, it is not. An old saying in the industry is "toxicology happens." Safety assessments provide an ideal opportunity to characterize the direct and indirect effects (if any) of the drug. As such, unexpected toxicity or technical challenges can serve a useful purpose, providing the team with

valuable insight as to unforeseen events and outcomes. The best thing to do in this situation is to start asking questions, both with the team and with your testing partners.

A drug development company can gain quite a bit of insight from these inquiries and reviews, which will ultimately shape both the characteristics of preclinical assessments and the First-in-Human (FIH) clinical trials. With the right partnership, working through this data can narrow the focus of safety testing when trying to understand complex molecules. Companies that ask an abundance of questions, even when feeling outside their realm of expertise, provide themselves the chance to have productive conversations and garner a stronger relationship with the safety assessment service providers.

Assessing Safety

Often due to constrained resources and occasionally by choice, most smaller drug development companies operate with a limited supporting team, which increases the risk for knowledge gaps to emerge – specifically when assessing the preclinical safety of a molecule. For example, if the makeup of a team's expertise is primarily in research and development, the focus of preclinical development skews toward investigating efficacy and proof of concept, resulting in the testing unintentionally overlooking some safety elements. If the team is well-versed in developmental biology and Good Laboratory Practice (GLP)-enabling *in vivo* study design but lacks relevant regulatory expertise, gaps in appropriate study designs and IND-enabling program content can occur. Investing in all of these critical areas is essential to minimize any delays of biology, safety or a regulatory agency's expectations.

Drug development companies need to prioritize and invest in an objective, well-defined plan to assess safety. The safety assessment plan should include a characterization of the molecule and a robust safety profile of its dosage level and regimen in the selected test systems. Drug developers need to account for testing surprises, which are inherent to comparative pathobiology and potential species-specific sensitivities. By initiating a safety assessment evaluation earlier and planning for surprises, the project stays on track for designated timelines in a proactive manner.

If assessing safety is out of a team's wheelhouse, finding an outsourced testing laboratory for one or more elements of the development plan provides a beneficial resource. These testing laboratories can act as objective partners to contribute an unbiased perspective and help develop a well-rounded study program. Testing laboratories willing and able to meet specific sponsor needs can deliver considerable value to small drug development companies.

The most effective testing laboratories free up drug developers' internal capacity to focus on what their experts specialize in and add expertise that isn't as strong internally. They can also customize their resource allocation to the individual needs of its customers and build credible associations with experts in the field of toxicology. In the eyes of regulators, this can engender trust that the data generated from the IND-enabling studies are true, accurate and compliant. Also, it is essential to use experienced testing laboratories when your drug is unique (structurally, pharmacologically and mechanistically) and when there may be specific regulatory and scientific considerations in the chosen path for drug registration (such as orphan diseases or first/only in class therapeutics for terminal diseases).

Evaluating Relationships

Outsourcing is an essential resource for drug development companies without access to a dedicated, internal laboratory. As the COVID-19 pandemic has disrupted production, supply chains and even international protocols and operations, finding a lab with the capacity, redundant systems management and access to the necessary resources can be challenging. Drug development companies should confirm that their current and future lab testing partners have plans and accommodations to mitigate or at least minimize these impacts through well-develop processes and procedures.

Approach the investment in outsourcing to a testing lab as establishing a true partnership, rather than enlisting a turnkey service provider. Drug development teams are most effective when they work closely with their partner organizations and function as a unit. Finding an outsourced testing lab that will approach the relationship in the same way can be a challenge, so it's best to do your homework when performing vendor assessments.

To identify an accountable, collaborative testing laboratory, start by understanding their core values and leadership. A testing lab's primary goal should be to help bring new drugs to market that will benefit the greater good. These laboratories should recognize that every project has a modest start, and small drug development companies make some of the most significant discoveries. These testing labs shouldn't allow larger contracts to take precedence due to the size of their expenditure. Laboratories that make even the smallest of drug development companies feel valued and supported throughout the process are worth the cost. Still, it's important to be transparent with your strengths and weaknesses so that all resources are brought to bear.

Selecting a Partner

Rapid, cost-efficient, and high-quality – these are the three common priorities in selecting a testing partner. As the selection process comes to a close, consider what the long-term impacts are when making any compromises in this triad. Don't forget what the financial implications could be if the testing lab does not treat the project with equal attention as they do larger clients.

Before signing on the dotted line, every potential client should ask the following questions:

1. Does this laboratory offer both scientific and operational resources?

An integrated partner can streamline the responsibility of the developer's primary point of contact by consolidating partners to one or two labs. Sharing data and results internally to a centralized organization typically becomes more efficient. Study timelines can also flex to respond to unforeseen needs since resources are ample. For instance, a lab can make up for adverse events that materialized during a study by adjusting schedules at another stage downstream. If a lab uses this study's results to select dose levels or final animal

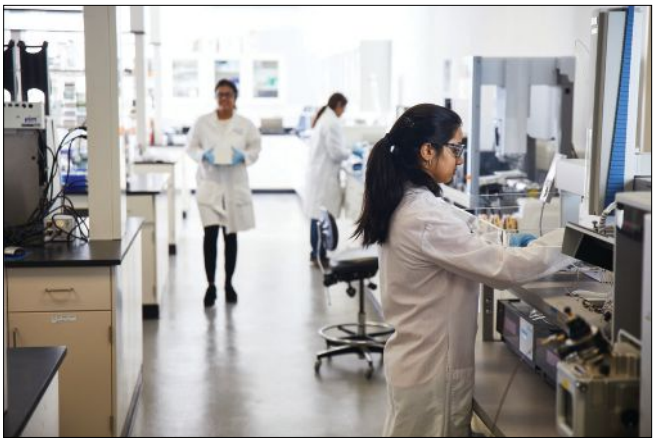
assessments in the pivotal, IND-enabling study, the testing lab can quickly adapt pre-study procedures to accommodate those changes. Finally, bundling testing programs to reduce costs, improve report timeliness and consistency of content, may better conserve budgetary resources, and potentially reduce the time spent auditing different testing labs.

Drug development companies who inquire about the cross-functional opportunities of an outsourced partner should vet the candidate labs for a range of capabilities inherent to the drug development program. From biomanufacturing, molecule characterization, production scale-up, analytical services, unique technical capabilities and more, the greater functionality and capabilities a testing partner's umbrella has, the more value they can deliver to a small team.

2. What is the lab's capacity and current access to scarce test systems?

The global pandemic's implications are far-reaching and unpredictable. Finding a lab with a proven response to protect their employees and deliver on timelines affords the security of keeping projects on track as much as possible. Some labs in North America are still enduring resource limitations and time constraints, so this may ultimately be the time for both small and large drug development companies to expand their consideration to international providers for preclinical safety studies.

On top of sufficient capacity, small companies need to find testing partners with adequate access to restricted tests and animal systems. Availability can be hindered based on international shipping barriers, and getting studies scheduled with hard-to-find test systems is no small feat. Even if a testing laboratory can accommodate testing programs that align with planned timelines, if they do not have access to models and finite resources, setbacks will occur. Delays



in study conduct can ultimately lead a company (with somewhat limited flexibility) to missing filing deadlines, resulting in a cascade of unfortunate events.

3. Does the lab have positive relationships with Regulatory Authorities?

An outsourced partner's regulatory compliance, in areas such as the U.S. Department of Agriculture, the U.S. Food & Drug Administration, animal welfare compliance and universally compliant GLP systems, is required. However, a testing laboratory's relationship with regulatory authorities is generally more complex and unique to each market. When it comes to these testing partners, evidence of a positive and constructive working relationship is seen not only in inspection reports, but also how responsive their quality systems are to the dynamic of oversight and change. As a whole, these relationships can impact a company's chance for successful submissions and approvals.

It is a common misconception that regulatory authorities are to be feared. Instead, drug development companies should view them as another critical partner in the process. Testing laboratories that work closely with both their clients and regulators can take steps to facilitate those relationships and improve your chance of success. This affiliation can assist a drug developer in getting ahead of evolving expectations and build credibility with salient regulatory bodies.

These relationships require a commitment of time, energy and resources both for the testing laboratory and the drug development company. Knowledge of regulatory expectations directly impacts the quality and integrity of the drug development program design and resulting data and reports. Gauging this needed competence will require some deliberate inquiries and time, so vetting for established connections can be a strategic advantage in creating a dialogue about the compound and testing program.

4. How does the audit process work?

In this exceedingly work-from-home world, many companies are not routinely traveling to perform the standard inspections of outsourced vendors. However, that doesn't make the need for assessing testing labs and service providers disappear.

Many companies have developed remote access systems for their clients, one of them being virtual facility audits. Even when different time zones are at play, vendors are going above and beyond to meet the needs of current and prospective customers. Whether that means creating a secure portal to review standard operating procedures (SOP) or staying after hours to meet the staff, vendors have developed new and creative solutions for the audit process in response to this need. The future obstacles presented by global events are unclear, and it's unrealistic to wait them out to find a lab testing partner. Testing labs and drug development companies are taking a new approach that can answer pressing questions from the safety of remote locations.

5. Is a scientific or regulatory consultant needed?

Many teams were stretched thin (whether it be capacity, personnel, expertise or experience) well before global emergencies. Now, conditions have amplified those challenges. Taking on too much responsibility can cost companies more in the long run than making the necessary investments upfront, whether that is committing the time for rigorous vendor assessment or securing adequate financial and scientific resources.

Be it a well-known testing lab that can manage complex programs or an independent consultant that can keep a team abreast of the latest industry and regulatory developments, small drug developers must recognize their gaps and find resources to fill them. Don't shy away from these opportunities. Many vendors either have the expertise internally or work with independent experts. When it comes to the latest guidance in areas such as biocompatibility standards for *in vitro* and *in vivo* testing, ignoring weaknesses can prompt regulatory setbacks if improper methods are applied; it's simply not worth the risk.

To successfully submit an IND application to the U.S. FDA (or to one or more global authorities), drug development teams need to proactively detail a clear plan with the end goal in mind: a successful, on-time submission to the agency and the ultimate approval for FIH studies. Carefully selecting the right contract provider can make all the difference in the ultimate success of the program. For many, these projects are a culmination of their life's work. In truth, everything starts small, and this is where the great discoveries have been made.

Moving beyond the preclinical safety assessment and development stage is a strenuous, costly process. In trying times, virtual, small and mid-size companies cannot be left behind. Their contribution to the progress and innovation of the pharmaceutical and biotechnology industry is invaluable, continually challenging the status quo, applying new and relevant technologies to improve the quality of our lives and communities. These companies should not feel neglected or alone in their efforts.

Critical Requirements of the Mid-Range Tablet Press

Frederick Murray, President

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Tablet press design innovation has traditionally centered on large-scale production equipment, however, there is increasing focus on the smaller-scale, mid-range models that must have the capability to support product development, scale-up, tech transfer, clinical batch manufacturing, small and medium batch production, and continuous manufacturing applications. This range of capabilities demands unique features and design flexibility.

A small-scale press must have the capability to work with a wide range of material quantities, from just 1 kg or less to batch sizes up to 50 or 100 kg. This requires the press control system to work effectively with a reduced tools configuration, where press tools are installed in every second or third station in the turret. This reduction of tools permits flexible operation with reduced material quantities and minimizes tooling investment in the development phase. Options to reduce the volume of the feeder are also required, including reduced volume feeder paddles, or a gravity feeder.

Small-scale presses must offer a comprehensive instrumentation package to permit real-time measurement and display of precompression force, main compression force, and ejection force. For bi-layer operation, the first layer tamping force also is a critical point of instrumentation. For product development, the press should have an on-board data acquisition and analysis capability that will collect high-speed data (press force versus time) and provide automated analysis to characterize force peaks, rate of force application, rate of force decay, area under the compression curve, and contact time. These parameters permit formulations to be assessed, optimized, and compared to established baselines.

Most small-scale presses are asked to do many things – so flexibility is paramount. Many applications require a single and bi-layer capability, and a fast-change conversion process that can be managed by the user directly. In combination with an exchangeable turret capability, the press can then produce a tablet of any size and shape, in a single or bi-layer format. A mixed turret, which includes both B and D punch bores and dies on the same pitch circle, provides the same flexibility in a reduced tools configuration, and without the need to execute a turret exchange. Finally, a small-scale press should offer some level of portability to accommodate those facilities where a dedicated room cannot be made available.

For small and medium size batch production, the ability to move quickly from batch to batch and product to product is a key consideration. If the press is being cleaned and retooled more often than it is running, which is often the case with older tablet press technology, the resulting efficiencies are extremely low. To facilitate a fast changeover, there are two key components that should be considered. First, an exchangeable turret, fully tooled off-line and ready to go, will dramatically reduce changeover times, while maximizing output for each product. For example, a small-scale press may offer a range of turrets, as follows:

Table 1.

Turret Specification	Maximum Tablet Diameter	Number of Punch Stations
TSM or EU D	25 mm	23
TSM or EU B	16 mm	28
TSM or EU BB	13 mm	34
TSM or EU BBS	11 mm	37

For a production portfolio that includes a wide range of tablet sizes, from 8 – 22 mm, for example, a single turret strategy would require the TSM or EU D turret, with 23-stations. While this turret would accommodate all tablet sizes, employing a multiple turret strategy would permit output gains for the smaller tablets, as follows:

Table 2.

Tablet Diameter	Turret Selection	Output Improvement
>13 and < 16 mm	TSM or EU B	22%
>11 and <13 mm	TSM or EU BB	48%
< 11 mm	TSM or EU BBS	61%

In addition to efficiency gains that may be realized from a robust turret exchange strategy, the use of fast change parts can also represent a significant opportunity to implement efficiency improvements. A well designed, small-scale press will have minimum parts to remove to facilitate a turret exchange, and smooth surfaces with good accessibility to clean the compression zone. Having a second set of product contact parts, including the feed hopper, feed pipe, feed frame, tablet take-off, and discharge chute – cleaned and ready to go – will streamline the changeover process. A parts cart, designed to ensure the repeatable position and placement of the product contact parts during disassembly and assembly, can also boost changeover efficiency.

As product containment becomes an increasing focus for tablet compression equipment, small-scale machines must offer comparable containment solutions. For medium containment requirements, an OEB 3 solution, which conforms to an OEL (Operator Exposure Level) of 10 – 100 µg/m^3, is most appropriate. Typical enhancements for OEB 3 containment include improved windows seals, tri-clamp connections for incoming material, and tri-clamp connections on the discharge chute outlets to permit contained transfer and collection of samples and tablet rejects. In addition, the compression zone should be configured with a differential pressure sensor that permits the measurement of negative pressure in the compression zone, which is then established as a run permissive. An inlet HEPA filter prevents any blowback to the room, in the event that there is an interruption of negative pressure, and more advanced systems may be configured with a motorized damper and a contained air handling unit, which will allow negative pressure in the compression zone to be controlled to a predetermined setpoint.

In addition, a split discharge chute design, in which the discharge chute is terminated in the compression zone and a transfer segment is mounted to the press window, ensures the contained transfer of tablets from the press. To permit contained access to the compression zone and facilitate manual intervention during operation, the windows of the press should be configured with interlocked glove ports and an RTP (Rapid Transfer Port) that lets press tools or small hand tools to be passed in and out of the compression zone without breaking containment. A manual vacuum wand in the compression zone, manipulated via the glove ports, allows the press zone to be cleaned before a manual mist can be applied to bind the airborne particulate. In most cases, PPE will be required to complete the cleaning process.

For higher levels of containment, including OEB 4 (1 – 10 µg/m^3) and OEB 5 < 1 µg/m^3), a full Wash-In-Place (WIP) execution with integrated isolator is required. This system also requires many of the same features as the OEB 3 execution, including tri-clamps and negative pressure control, but is further enhanced by the use of 316L stainless steel components and water-proof electrical components suitable for the wash-in-place environment. A WIP skid, which can provide heated water with multiple detergent options, is often employed, and the WIP recipe is established and executed via the tablet press control system.

For all containment solutions, an integrated approach is required in which the complete system – consisting of the press, deduster, metal check, tablet tester, containment valves, WIP skid and air handling system – is integrated with all make-break connections and valves and, for operation ease, managed from a single HMI.

For utilization in a batch production mode, for clinical manufacturing or small to medium batch sizes, the small-scale tablet press must have a full production-scale control system. This means secure operator login and authentication, electronic audit trails to track machine adjustments, alarms, and tablet rejects, as well as secure batch data handling to ensure full compliance with 21 CFR Part 11. A press force control system, which permits automatic tablet weight control by monitoring the compression force and making precise adjustments to the dosing cam, also is a critical requirement of the small-scale press control system. The press force control system must also facilitate automatic layer weight control when operating in bi-layer mode. A single tablet rejection capability, based on the monitoring of individual press force values, will reject and record the punch station of every rejected tablet over the course of the batch, as well as identify problematic tool stations.

For a higher level of automation, the press control system should permit a seamless interface to peripheral devices surrounding the machine, including an overhead feed system or post hoist, tablet deduster, metal check, tablet diverter, tablet collection system, or in-line tablet tester, which will automatically sample and measure tablet weight, thickness, and hardness in real time. Finally, the control system must offer a network integration capability to support product recipe management, secure batch data storage, and the transfer of process data to a central SCADA system or historian.

The use of Industry 4.0-capable sensors and the integration of on-board diagnostics is also critical, especially in product development settings where immediate maintenance support may be limited. Another key feature for the small-scale press is a control system HMI with on-board help, including access to manuals, electrical schematics, spare parts lists, assembly drawings, work instructions, and procedural videos to support the machine setup, turret exchange, and machine changeover.

The small-scale tablet press is generally the machine of choice for continuous manufacturing applications, as the output capability aligns with typical process requirements. For this special application, the press should permit the integration of NIR or RAMAN sensors to yield real time, in-line measurement of content uniformity. These sensors are often placed in the material feed pipe or, preferably, directly in the feeder where the dies are filled. These sensors provide feedback to the supervisory control system, which may then access the tablet press control system to direct the flow of tablets to the good or reject channel. The supervisory control system should also be able to download product recipes and make in-process adjustments to the dosing cam or tablet thickness settings while the machine is in operation. Success in a continuous manufacturing line requires an open control system architecture that supports seamless integration of the tablet press to the central, supervisory control system.

Given the many ways that small-scale tablet presses are required to operate, it is clear that sophisticated technology is required – to ensure that the press has the flexibility and capability to work effectively and efficiently in a diverse range of production environments and applications.

Frederick Murray, President of KORSCH America Inc., a leader in tablet press technology offering solutions for product development, scale-up, high-speed production, multi-layer, mini-tablet, and WIP/high-containment applications. www.korsch.com

Adeno-Associated Virus (AAV) Vector Gene Therapy - From Idea to IND

Vibhor Gupta, Ph.D. and Jaleel Shujath, MBA

Absorption Systems

Gene therapy holds enormous promise, revolutionizing the way we approach and treat diseases, including many that were previously considered incurable. The global trend for expansion continues, with more than a thousand cell and gene therapy (CGT) clinical trials underway in 2019.[1] Whether it is an introduction of genetic material into target cells *in vivo* or *ex vivo* (cell therapy), Adeno-Associated Viruses (AAV) have strengthened their position as a leading platform for gene delivery especially after recent landmark approvals: Luxturna (voretigene neparvovec), an AAV-based therapy that delivers a functional copy of the RPE65 gene to patients with vision loss due to mutation-dependent retinal dystrophy, and Zolgensma (onasemnogene abeparvovec-xioi), which harnesses an AAV (serotype 9) vector to deliver a functional copy of the SMN1 gene to motor neurons in spinal muscular atrophy patients. The pipeline for AAV vector-based therapy is also increasing, with at least 250 clinical trials conducted during 2019.[2]

AAV vectors are promising gene delivery vehicles because they have an excellent safety profile (they rarely integrate into the host genome). They can transfect both dividing and non-dividing cells, have broad tissue tropisms, the ability to transduce multiple species, and achieve sustained and high-level expression. However, AAV vectors have limited packaging capacity (4.7 kbp), and despite being the least immunogenic therapeutic viral vector, AAV can evoke anti-drug antibodies (ADAs), which may be either pre-existing or developed after the onset of treatment, and this can limit effective gene transfer and nullify transgene expression. Several approaches to AAV vector engineering offer solutions to its limitations and also improve its potential as a gene delivery platform; for example, the inverted terminal repeats (ITRs) can be modified to make them self-complementary, increasing transduction efficiency, and the transgene can be codon-optimized for better protein expression. Both approaches reduce the host anti-AAV immune response.[3]

As companies transform a gene therapy idea theorized in a lab, from bench to bedside, timely filing of an Investigational New Drug application is the first vital milestone. Here we discuss how to design *in vitro* and *in vivo* studies effectively and highlight common "roadblocks" that might delay the Investigational New Drug (IND) submission, strategies to overcome them and focus on specific considerations for AAV-based therapy. Current regulatory guidelines and the expectations of regulatory agencies will be emphasized throughout.

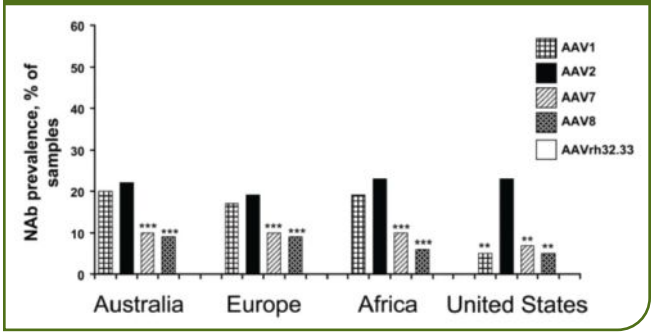
Early Phase Product Development – What to Consider?

Essential questions in early-stage product development are capsid/serotype and expression cassette selection and the impact these decisions might have on manufacturing and scale-up of the product. The choice of AAV serotype is crucial; both tissue tropism and clinical endpoints must be considered. Typically, capsid/serotype selection is based on effective gene delivery in preclinical animal models. However, these do not always accurately predict the human outcome. The use of chimeric (human/mouse) models can help to overcome the species-based discordance in gene transfer and better predict clinical relevance.[5] Pre-existing human immunity can also influence the choice of AAV serotype. The prevalence of different anti-AAV neutralizing antibodies (Figure 1) varies according to geographical region.

Therefore, if there is intention to work with a novel AAV serotype, ensure that a human population sample is screened for pre-existing immunity. Our experience indicated that a significant hurdle for assay development and validation was sample availability. Carefully assess how to obtain representative human serum and plasma samples if this type of screening is required. If multiple AAV serotypes are being screened, then the number of samples required rapidly becomes burdensome. A representative pooled sample could be used if the pool does not contain significant outliers.

Each AAV serotype has a particular tissue tropism, leading to AAV-specific biodistribution. AAV-2, for example, does not readily transduce the liver. However, AAV-9 has a broad tissue tropism, including reproductive organs, which could raise safety concerns regarding vertical transmission. The systemic injection of AAV provokes a more

Figure 1. Worldwide Epidemiology of Neutralizing Antibodies to Adeno-Associated Viruses
The Journal of Infectious Diseases, Volume 199, Issue 3, 1 February 2009, Pages 381–390, https://doi.org/10.1086/595830



significant immune response than other administration routes and there are serotype-specific differences in clearance. AAV-9 persists in the circulation longer than other serotypes.[6] Viral scale-up is also serotype dependent. AAV-6, for example, has a poor overall yield that is at least four-fold lower than AAV-9.[7]

Expression cassettes have multiple components that must be optimized for high and sustained protein expression. Promoters drive transgene expression and can be selected to dictate the location (ubiquitous versus tissue-specific promoters) and temporal (regulatable promoters) expression of target proteins. Ubiquitous promoters produce high levels of target protein, but this may provoke a robust host immune response, limiting gene expression.[8] Tissue-specific promoters are physiologically relevant, allow systemic administration and may induce immune tolerance.[9] Large promoters such as CBA or CAG can account for up to 36% of the AAV total packaging capacity, potentially limiting the size of the transgene. Other components of an expression cassette, such as poly-A, other regulatory elements, enhancers, or introns should also be optimized, as they can have a direct impact on protein stability and expression. The transgene may be a native, foreign, or chimeric protein and will have a significant impact on the overall immunogenicity of the vector. The biology of the expressed protein is also fundamental. For example, a growth factor might be oncogenic if expressed at a supraphysiological level. Also, performing *in vivo* and *in vitro* assays in tandem is critical for product design because there are instances when *in vitro* assays do not accurately predict *in vivo* responses.[10]

Chemistry, Manufacturing and Control (CMC) Assays

To set out some of the potential design challenges and to illustrate how the final product design influences our approach to these assays, we will examine the design and characterization of a critical CMC assay, the *in vitro* potency assay, which is an absolute requirement for clinical lot release. According to the compliance guidelines, these assays must be conducted *in vitro* for the biologics license application (BLA) submission.

The cell line chosen for an *in vitro* potency assay must be permissive for the selected AAV serotype and promoter, biologically relevant for the target gene so the mechanism of action can be evaluated, have low endogenous target protein expression, and have good growth characteristics. These complex choices are illustrated in the following case study. In rhodopsin-dependent retinitis pigmentosa, the afunctional rhodopsin protein can have associated toxicity. Cideciyan *et. al*., has developed a product with dual function: an AAV-5 vector overexpressing functional rhodopsin and shRNA designed to silence mutant endogenous rhodopsin proteins.[11] Designing an *in vitro* potency assay for this vector is demanding since one of the genes of interest is an ion channel with complex biology. AAV-5 intrinsically has a low *in vitro* transduction efficacy, and the promoter is tissue-specific. Therefore, an AAV-5 permissive retinal cell line that allows monitoring of rhodopsin's mechanism of action is required to develop an *in vitro* potency assay. Theoretically, such a cell line can be developed, but the timeline should be considered to keep the end goal in mind. Similarly, some therapeutic genes like human RPGR (retinitis pigmentosa GTPase regulator), which has been a target to treat XLRP (X-linked retinitis pigmentosa), may pose some unique challenges when it comes to developing a potency assay, as RPGR has no well-known biological mechanism of action that can be used to develop an *in vitro* potency assay.

Not just a potency assay, but the development and validation timeline of other CMC assays like an infectivity assay should also be considered, especially in light of the lack of published guidelines. Should primers/probes be designed for generic (e.g., ITRs) or target-specific sequences? Should techniques like ddPCR or qPCR be used? Should only assay formats like TCID50 or transduction be employed? All these questions, when not answered well in advance, can impact the timeline for IND submission. Therefore, we advise meeting "early and often" with regulatory agencies to determine what is appropriate for individual products.

There is no well-defined set of best practices for developing and manufacturing an *in vivo* gene therapy. The Alliance for Regenerative Medicine has brought together more than 50 experts with the aim of providing a central standard for design, development, and scalable manufacturing strategies for gene therapy. The proposed document (Project A-Gene) uses an AAV gene therapy case study to illustrate how these strategies can be implemented, and it is scheduled for release in summer 2020.[11]

AAV can be manufactured and scaled by mainly three different methods (Figure 2), which have inherent advantages and disadvantages. For example, helper virus-based methods are advantageous in that they are suspension cultures that facilitate scale-up. However, the final product may be contaminated with the helper virus. Ensure that appropriate planning occurs for the manufacturing modality of choice.

Intellectual property might not be an obvious concern in early-stage planning. Still, it is vital to determine whether any proposed vector components are subject to any licensing restrictions. The Regenex

Figure 2. AAV vector production strategies – Pros and Cons[12]

Production Strategy	Advantages	Technical Disadvantages	Commercial Disadvantages
Helper Virus	• Scalable suspension system. • Serum free media can be used for production.	• Helper virus contamination • Long lead time for cell line and virus seed generation. • Increased purification & analytics required.	• Expensive cell line licensing. • Large Cost investment. • Long clinical production time.
Baculovirus	• Scalable suspension system. • Serum free media can be used for production.	• Baculovirus contamination • Long lead time for cell line and virus seed generation. • Increased purification & analytics required.	• Expensive licensing for cell line. • Large Cost investment • Long clinical production time.
Helper-Free Transfection	• No helper virus contamination. • Rapidly transient production. • No/low licensing required.	• Scale out rather than Scale up. • Requires serum containing media. • Low Productivity	• High costs for scale out (labour, materials, facility)

Bio NAV technology platform holds exclusive rights[13] to multiple AAV serotypes, including AAV-9. Failure to recognize this could result in substantial licensing costs in the future. Similarly, promoter- or codon-optimized transgenes could be patented. Cell lines that form the basis for commercial release assays and technology like ddPCR may also have restrictions or licensing issues.

Designing Preclinical Studies to Enable IND Application

Pharmacology studies provide proof of concept data for expression/activity of the protein of interest over time, preliminary information about the optimal route of administration, dosing, and evaluate the efficacy of both the vector and transgene. The FDA recommends selecting an animal species that demonstrates a biological response similar to humans. Some of the critical factors to choose an appropriate animals model are: does the animal model allow vector transduction, is the gene of interest pharmacologically active in the model, is there pre-existing immunity, and could the transgene trigger an immune response in the selected species?

Toxicology studies assess product safety and support proposed clinical investigations. Humoral and cellular immunotoxicity, genotoxicity (genome integration), and reproductive toxicity (e.g., vertical transmission of AAV virus in germ cells) must be assessed. Shedding studies assess horizontal transmission. The FDA requires that all safety studies should be GLP compliant; however, if any toxicity studies are non-GLP, ensure that you include evidence to support why this decision was taken, what other complementary studies were performed under GLP, define the quality system used, how the data was recorded and archived, and include all of this information in the IND package.

Optimizing Regulatory Interactions to Ensure a Successful IND Application

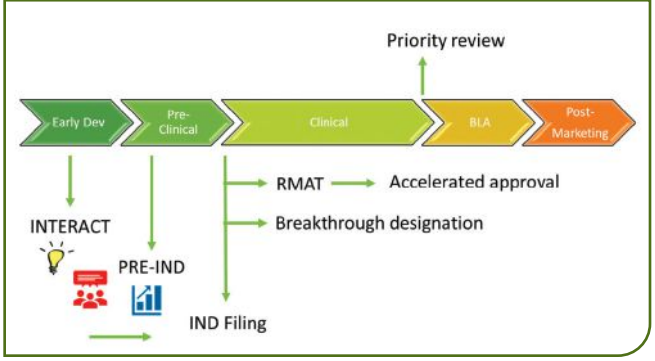
The initial meeting with the FDA is called an initial targeted engagement for regulatory advice on CBER products (INTERACT) meeting. Its primary goal is an early discussion before the pre-IND meeting and serves as an opportunity to discuss *in-vitro* assays, pharmacology, and toxicology study design. This interaction is an ideal opportunity to identify design problems before embarking on these experiments. When you have a complete or partial preclinical data set, a pre-IND meeting can be requested. During this meeting, you can discuss your results, strategy, and approaches to obtain FDA support. These types of discussions help to identify and avoid unnecessary studies. The FDA will provide written constructive feedback. Naturally, incorporating this feedback is crucial and avoids the possibility of a potential clinical hold in the future.

The IND application includes the nonclinical data, manufacturing conditions, and clinical protocols. All of this information is available on the FDA website. Ensure to have checked any updated regulatory guidelines, forms, and flow of the process before assembling the IND package.

Regenerative medicine advanced therapy (RMAT) designation is for drugs that are intended to treat or cure severe and life-threatening diseases. If you fulfill this designation, then your program has eligibility for increased early interaction with the FDA, priority review, and accelerated approval. The timeline of interactions with the FDA and accelerated pathways are represented in Figure 3.

The FDA also offers multiple expedited review programs to promote rare disease research. You can apply for all of them based upon the phase of product development. For example, you can apply for breakthrough designation during IND filing, and priority review during new drug application (NDA) or BLA filing. All these programs have multiple financial advantages. Orphan drug designation programs provide seven years of market exclusivity, tax credits,

Figure 3. Timeline of FDA filing and expedited review



filing fee waiver, and additional assistance from the Office of Orphan Product Development. Similarly, rare pediatric disease priority review is a special program for rare diseases in the pediatric population.

The road to approval is challenging but risks can be mitigated through careful planning. Whichever strategy to product approval is ultimately chosen, keeping the end in mind will often provide the best outcome.

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Decentralization: A Direct Approach to Clinical Trials

Nicole Gray

Director, Strategic Supply Solutions
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The global COVID-19 pandemic has had a significant impact on all our lives, forcing us to adapt and find creative ways to continue our day-to-day lives. Clinical trials are no exception and have had to face many new challenges. Due to local lockdowns, patient and site staff safety, and personal choice, some patients have been unable or unwilling to travel to their clinical site and in some cases, clinical sites have had to close completely. Clinical sites and sponsors have had to quickly implement solutions. This new way of life provides an opportunity for the further decentralization of clinical trials, with Direct to Patient (DTP) reducing or eliminating the need for patients to travel to clinical sites and potentially expose themselves and others to a risk of infection.

Even before COVID-19, decentralized trials offered many potential benefits to clinical sponsors and sites, including: broader patient access and demographics; opening trial participation to patients in remote areas and reducing the geographic barriers; assisting with recruitment and patient retention; and increasing access to patients with rare diseases. They may also help to decrease overall trial costs by reducing the need for investigator and site staff to dispense investigational medicinal products, and the need for storage at clinical sites.

Although they are only now receiving more attention, decentralized trials have been carried out successfully since the 1980s. Whereas traditional centralized clinical trials are conducted at designated study sites, and all procedures are generally performed by investigators and their delegated personnel, technology has opened the way for decentralized models, in which some or all study-related procedures take place away from the investigator site, either via telemedicine or through local healthcare providers, such as primary care physicians, pharmacists, clinics, home-based care or even a regional hospital. Smartphones, tablets, web browsers, access to tele-visits and electronic medical records are making it easier for patients and study staff to communicate and stay in touch in real time. With these advances in technology, the potential benefits are significant.

In a decentralized trial, clinical investigators remain the lead medical professionals conducting the trial, and it is under their authority that the drug is dispensed and administered to a patient. Even if no patient ever visits it, there is still a physical clinical site where the investigator conducts, receives or coordinates all trial-related activities.

Different Approaches

The industry refers to direct-to-patient as all inclusive, and encompassing Site-to-Patient (STP) supply, where the clinical site arranges and ships the product to the patient's home or chosen location from inventory held at the clinical site. True direct-to-patient bypasses the clinical site and the product is dispensed directly to the patient's chosen location, usually their home or workplace, via a pharmacy. Ideally, the solution will take a hybrid approach allowing the patient and investigators to make the best decision for their unique situation. A best practice, flexible solution would allow for STP and DTP to apply to either all shipments for all patients, some shipments for all patients, some shipments for some patients, or in emergency situations only, depending upon how the approved study protocol is structured. If such flexibility is desired, sponsors must carefully evaluate potential DTP partners with this possibility in mind as not all have the necessary capabilities or infrastructure required to support this type of approach.

Studies can be set up to meet the needs of the patient population and the protocol. If possible, and if the trial design allows for it, patients should be given the choice of telemedicine visits or in-person site visits. Older patients generally express a preference for site visits, while younger patients prefer a telemedicine experience. Flexibility in the protocol design is key: the more options available, the better the experience will be for the patient.

Direct-to-Patient Studies

Direct-to-patient distribution is a very patient-centric approach that takes into account each patient's quality of life and can remove some of the complexity and burdens of participating in a clinical trial, particularly if traveling to a clinical site would involve a long and difficult journey. In a 2014 study by ISPE (International Society for Pharmaceutical Engineering), approximately 78% of patients indicated it would be very helpful to have their medication delivered to their home rather than traveling to a clinical site.[1]

There are also numerous benefits of a decentralized trial to sponsors. First, it broadens patient access and the demographics available to the trial by allowing greater participation for patients in remote areas. This is particularly important when the trial involves a rare disease, where the target patient population is sparse, and it would ease some of the difficulties associated with recruiting patients from all over the country or all over the world.

Logistically, a decentralized trial that uses a true direct-to-patient versus STP model reduces the need for many physical site locations, as well as reducing the storage burden on the clinical site, as the investigator's staff are no longer responsible for receiving, storing and physically dispensing the product.

While managing drug supply is a critical component for decentralized studies, it is not the only important consideration that sponsors must address. For example, the structure of these studies must also ensure they adequately support patient compliance and adherence, often using e-technology. The use of technology such as smartphones and access to tele-visits in conjunction with home health care providers, nurses, mobile phlebotomists and other local healthcare providers, are all part of the decentralized trial solution.

Another benefit is that DTP might alleviate product stability concerns resulting from patients transporting the drug from the clinical site to their home. Direct delivery ensures that the drug is kept at the appropriate temperature conditions and fully monitored throughout the supply chain. When all these advantages are considered, it is possible that the improved efficiencies introduced into decentralized trials using DTP distribution could reduce the overall cost of the trial by reducing drug waste and supporting patient recruitment and retention efforts to help studies stay on budget and progress according to plan.

However, DTP distribution of clinical supplies is a complex endeavor that goes far beyond just changing the shipping destination of the patient kits, and there are several important aspects related to the packaging and delivery that need to be addressed before a DTP study can be implemented.

Perhaps the most important components of a successful decentralized study are the patients themselves and their ability to store and take their medication as instructed and complete any necessary self-reporting or other data-generating activities. Prior to offering a DTP option, sponsors must gauge whether patients will have an appropriate level of support to ensure successful administration and

reporting in an at-home setting. Patients will need to be given clear instructions on when to start taking the medication, and on when and how to contact their doctor or clinical site for any questions related to their treatment or to report an adverse event. A virtual visit or check-in with the patient on the scheduled date of delivery is best practice, while understanding of procedures can be assessed by a questionnaire or checklist.

The stability of the drug is a critical consideration, and a plan must be put in place to determine how temperature excursions will be detected and handled. For example, if a patient receives a shipment that has been subject to an excursion, the sponsor will need to decide during study set up, whether the product should be left with the patient or automatically returned to the clinical site or pharmacy that dispensed it and a new shipment expedited to ensure that the patient's treatment plan is not disrupted.

Sponsors must put clear guidance in place regarding how the clinical site will document the receipt of the product by the patient, that it was the correct product, that it arrived in good condition and that the patient is clear on protocol instructions. Again, a possible solution would be a virtual tele-visit on the scheduled day of delivery to review the receipt with the patient and to ensure the product was received in good order. Provisions must also be made for the reverse logistics needed to ensure that unused study drug is returned, reconciled and eventually destroyed.

Data Management

Data management considerations are another crucial factor, and the choice of the interactive voice response (IVR) system can have a direct impact on a sponsor's ability to offer direct-to-patient distribution of clinical supplies. Unlike exclusively clinic-based studies, where certain personal patient information is not needed in the IVR, decentralized studies using DTP distribution may require additional data to be held, such as a patient ID number and/or a patient's city, state and zip code. Not all IVR systems can be configured to capture this information.

Furthermore, while some IVR systems are designed to be flexible, others are less so. A lack of flexibility within a system may make it difficult or impossible to switch patients during a study between receiving their treatments in a clinical setting and receiving them at home. This may require manual workarounds and extra work for the clinical sites and it is recommended that the study is set up to be flexible from the beginning. For sponsors who already have an IVR in place, understanding potential system limitations is necessary to determine if a current study set-up can accommodate a DTP option.

Sponsors should also consider how the IVR will be updated. For instance, the dispense date is the date the patient receives the medication, and not the shipment date. The IVR will need to be updated when the patient receives the medication, to ensure that the correct dispense date is logged. A decision will need to be made as to who updates the IVR and how this will be done.

Packaging

The packaging configuration for clinical supplies for use by patients in a home setting is another important consideration for sponsors, especially if the patient will not have support from a visiting nurse or other home healthcare provider. For example, the patient must be able to understand and manipulate the packaging and access the drug, so special packaging characteristics may be needed for use in an at home-setting, such as senior-friendly or child-resistant packaging, that would not be necessary in a clinical setting. Additional visual cues may be needed to provide reinforcement that a dose was taken, such as an empty blister cavity or a time-of-day/day number indicator.

The packaging should be of a size, shape and volume that will enable the patient to store it as directed. And if additional components designed for use by patients are required for at-home use, such as an instruction sheet or checklist, these materials will need to either fit into the drug packaging or shipping container or be sent separately. Sponsors should plan their clinical supplies with this in mind.

The Future of Decentralized Clinical Trials

Most clinical studies outside the United States have been site-to-patient. In Europe, direct-to-patient distribution is possible and has been done, but it is dependent on sponsor protocol and patient population and requires approval in each country. Local laws also need to be considered, and a separate supply plan should be put in place for each country to maintain flexibility; these supply plans can then be amended as needed rather than having to redo the entire protocol.

COVID-19 has significantly changed the landscape for clinical trials. Regulations and approval processes have changed rapidly over the past few months, with some countries relaxing their regulations to maintain patient access to critical medications. It remains to be seen if these changes are temporary or will eventually become permanent, but it is likely to open up more possibilities for future studies.

Now, more than ever, STP and DTP services have benefits for patients, sponsors and clinical sites. The COVID-19 pandemic and the consequences it has had on people's lives and trial logistics has caused many more sponsors to now plan for inclusion of some form of DTP in their future and ongoing protocols. The US FDA has stated that it supports decentralized trials and the expansion of patient access through digital health technology,[2] and has produced a lot of guidance to date.

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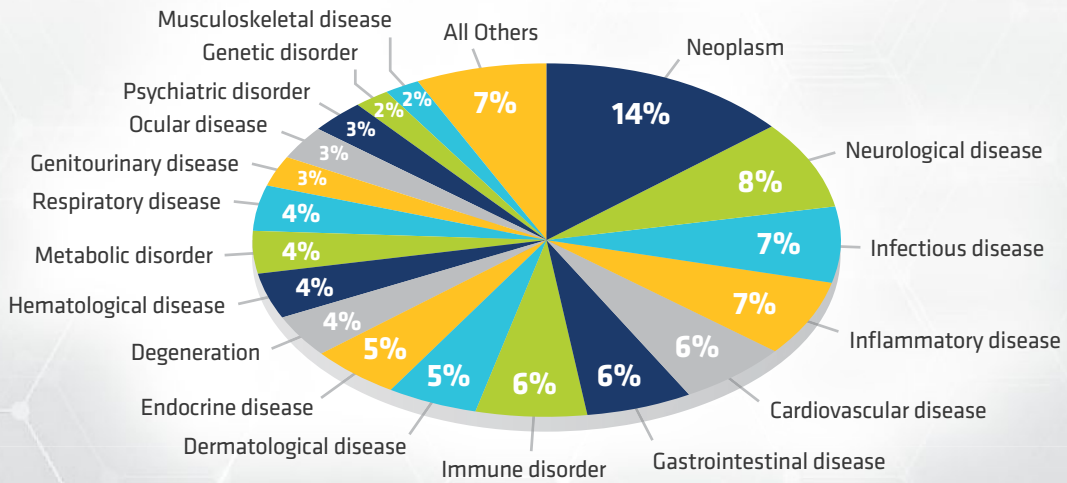

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The Importance of Effective Data Capture and In-Lab Tech for Bioanalytical CROs: Implications for Quality and Customer Satisfaction

Graeme Dennis, Commercial Director

Preclinical Pharma
IDBS

Asked about obstacles that make them second-guess outsourcing work to bioanalytical contract research (CROs), pharmaceutical companies do not mince words: "regulatory compliance and scientific expertise," and "unresponsiveness and imprecise data"[1] are among the more cutting remarks. This is not what prospective customers need to hear. In a highly competitive industry where compliance, quality, and integrity are critical to winning and retaining business, pharma sponsors must have high confidence in their CRO partners.

Meanwhile, early drug discovery and preclinical testing remain among the most labor-intensive phases of the drug development cycle. With just one in 5,000 compounds that enter preclinical testing progressing to clinical trials, rigorous processes and expertise that effectively orchestrates these phases is essential. This crucial capacity, both specialist and labor intensive, is fueling the current rise in the global preclinical CRO market, which is expected to reach $7.8 billion by 2027, registering a CAGR of 8.3% over the next seven years.

Bioanalytical CROs able to drive effective bioanalytical workflows, from sample preparation to analysis and auditing, stand to gain the most over the forecasted growth period. But there are many factors that determine the value of CRO partners, and the solution to improving each of them lies in technology, especially in the Quality department.

CROs themselves face challenges: an explosion in sample volume, a cost-sensitive market, tight turnaround times, an increasing diversity of assays, and a need to demonstrate regulatory compliance and build their credibility. They have encountered a market-driven demand, simply put, to do more, for less, faster, and more reliably.

Within the CRO, priorities further vary, depending on the point of observation. Bench scientists seek tools to refocus their work on method execution, managing or eliminating deviations, and improving collaboration. IT leaders naturally emphasize digital transformation with demonstrable ROI, in particular where a more efficient use of resources can be gained. And executive management is bottom-line focused, seeking means to minimize cost and maximize yield while reducing need for additional equipment or headcount. They'd like to reduce project times and invoice faster as well.

A software approach further recognizes that, typically, people aren't the problem – in fact they're a CRO's greatest asset. Attempting to push the compliance burden to people and paper (or spreadsheets), while appearing to require the least change management and outlay, in fact cripples a research operation. The opposite of the desired outcome results. Pushing audit trail construction, QC reporting, directly impacts sample throughput and introduces uncertainty, compared to what can be achieved in digital systems. It is rarely billable work and it is time consuming.

April Pisek, an experienced bioanalytical science in the contract research space and solutions consultant at IDBS, expanded on what a multi-layered quality system can do for confidence in data and offers a five-step model to drive expectations: "First, engineer quality-by-design before the data is even entered into the system, reducing manual, subjective, and laborious QC processes. Second, build detailed audit trails that are not only thorough, but user friendly and human readable. Third, provide the ability to reconstruct data in an instant to get to insight or impact assessment. Next, design a validated ability to aggregate information from the source of truth thus eliminating QC review. Lastly, design a data model that has intention and purpose to serve Quality teams while allowing remote auditing from anywhere in the world."

Operationalizing quality-by-design is a further expectation to put on software. Today's best systems blur the line between electronic lab notebook (ELN), method execution, sample management, and quality management. As such, method execution support is a baseline capability against which to evaluate solutions. This introduces consistency in execution, supports onboarding and training, and permits flexible use of staff across projects. User qualification and conditions for material handling can be similarly enforced. As such, the software supports knowledge transfer, both internally, and ideally from sponsor to CRO, a known and frequent pain point. Parameterizing processes in this way helps CROs ask the "right questions" to achieve consistency. Finally, data governance can be operationalized in software.

This last point about data governance is critically important. Organizations leaning in on data strategy understand the key role of governance. They convene data governance groups to debate and set standards for adoption, and perform data stewardship functions. However, data governance that heavily relies on individual compliance does not tend to work out well. When business rules are set and enforced in software (or best of all applied at the moment of data acquisition in a thoughtfully-designed integration), data requires no further manipulation to be "reporting-ready."

No discussion of this type should be complete without an accounting of the efficiency gains yielded by adoption. Fortunately, they can be tied to specific tasks in the bioanalytical workflow. Non-bench tasks relating to data management are consistently shortened (see Figure 1). This technically enabled workflow includes the integration of reagent and buffer preps, the broad adaptation of barcodes for consumables, reagents, and instruments, the capture of deviations from method at the point of entry, and documentation in real-time. Real-time equipment verification incorporates compliance and prevents common errors such as capturing the use of incorrect materials or equipment.

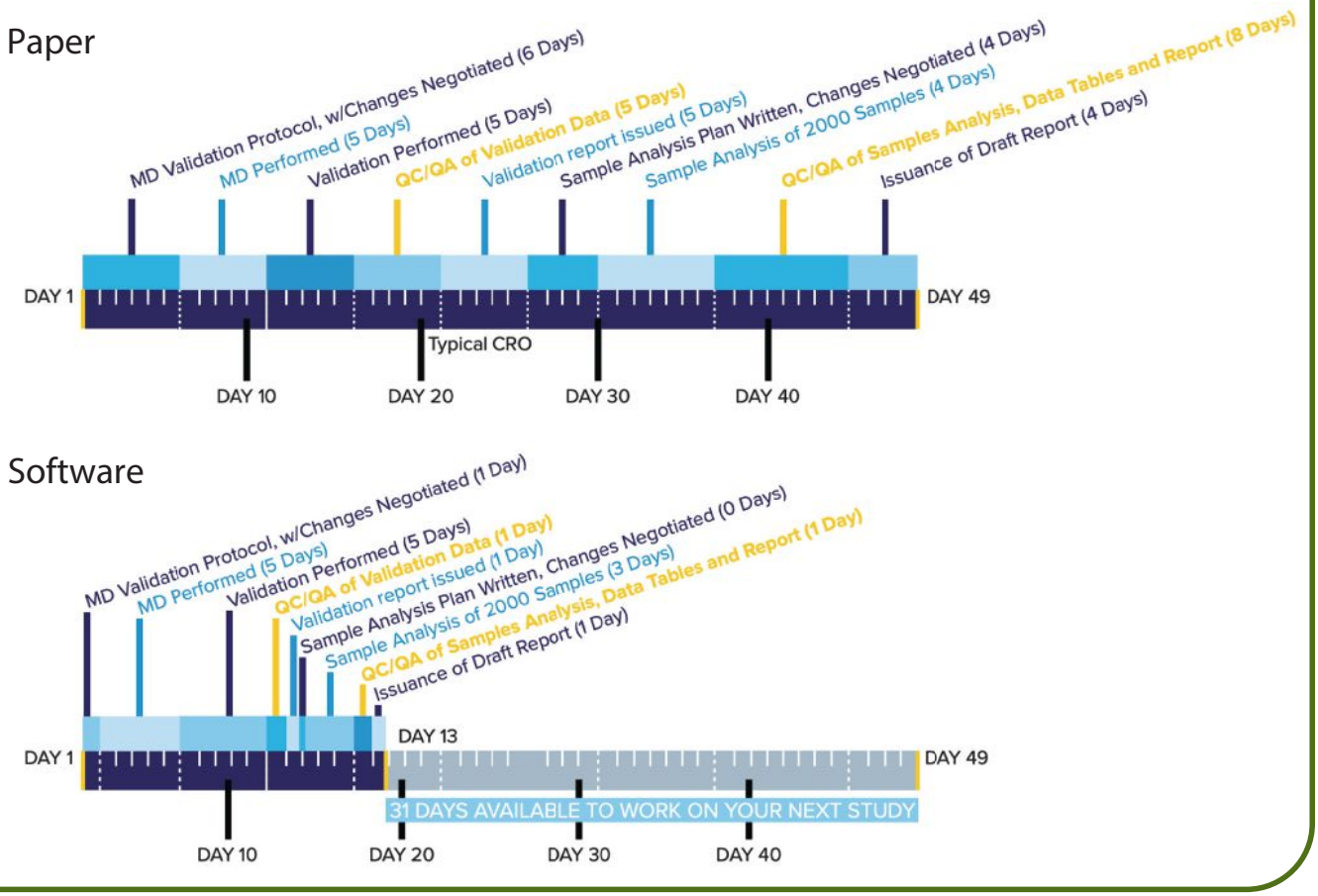
In the paper scenario, challenges drawing the study time to 49 days in the small molecule analysis workflow examined can be reduced to two principal root causes: difficulty in locating and discerning data for inclusion in a report or a retrospectively constructed audit, and processes with a dependency on a single individual. The software-mediated counterpart yields a 75% reduction in QA overhead, or thirty days of work in the small molecule analysis illustrated.

CROs today seek competitive advantage in a globally competitive market, facing the challenges outlined above. This can be described as "What a Winner Looks Like." When seeking to attain the advantage that well-architected software offers, CRO leaders can expect to win by:

1. Increasing the number of studies and samples tested, opening potential to take market share.
2. Removing the need for new people and equipment to meet demand, controlling operating costs.
3. Tightening study turnaround time and proving quality of results, exceeding sponsor expectations.
4. Reducing the effort and time to demonstrate regulatory compliance in practice.
5. Building credibility by powering the business with industry-recognized software and services: a "halo effect".

We've only briefly mentioned instrument integration as a feature of this data capture strategy. To be clear, integration is a pillar of any modern scientific informatics solution. Historically, tools in the ELN class have focused on data capture by any means, be it unstructured, structured, harmonized with other data, or consistent with a broader standard – anywhere, along a data maturity model. This is the general concept of "paper replacement" or "paper-on-glass" ELN. Untold exabytes of semi-dark data exist in this state, awaiting remediation or transfer to another database structure which may (or may not) permit it to become the source of further insight.

Figure 1. Study timeline impact of a software-mediated method execution and quality process



Today's scientific informatics customer expects much more in terms of the capture and presentation of data that can provide not only the basis for operational insight and reporting, but strategic insight that offers process understanding and enables *kaizen*. CROs that have this kind of relationship with their sponsors evolve from service provider to full, trusted partner.

While this article focuses on the challenges and benefits to quality processes at a bioanalytical CRO, the core messages may be transferred and amplified in the contract manufacturing organization (CMO)/contract development and manufacturing organization CDMO) spaces. There is real urgency to obtain not only operational and regulatory support from software systems in manufacturing, but the kind of strategic insight that supports digital twinning and process optimization.

When workflow design anticipates integration and quality needs – what Pisek described as "intention and purpose" of the system – then the data presentation for reporting and greater insight is *much* less burdensome. This is probably the most important learning of the 2010s in scientific informatics, and lead to a pivot toward the uses of data downstream from the moment it is acquired. For so long, these systems were about data capture, period. The most forward-thinking players in our industry think, where does the data go *next*?

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Planning for Success in Early Phase Clinical Trials

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Early phase clinical trials are becoming increasingly complex, potentially leading to a higher risk of failure. But careful planning and attention to some key areas in the early phase can mitigate the challenges.

Improving experimental drug success rate and accelerating clinical development are top priorities for pharmaceutical and biotech companies, and careful decision making is essential to minimize development time, manage costs and improve the probability of commercial success. There are a number of areas where clear focus and attention to detail can optimize the clinical development process.

The principal aim of early phase clinical trials, known as human pharmacology studies, is to collect information on the safety and tolerability of the drug product. When planning a first-in-human (FIH) trial, a carefully tailored design is essential for safety and further decision making. This is also the first opportunity to assess the pharmacokinetics (PK), and potentially the pharmacodynamics (PD), of a compound in humans. Most FIH trials are randomized, double-blind and placebo controlled, but many other decisions about major practical aspects of the protocol are based only on pre-clinical data. These decisions may include whether the compound should be tested in healthy volunteers or patients; how many dose groups and subjects are needed and whether these should be run sequentially, or in cross-over; what the safe starting dose should be and how it should be escalated; how long the follow-up should be; and whether there is added value in using an integrated protocol testing a food effect, drug interaction or special populations.

Modeling and Simulation

Modeling and simulation can help drug developers to better plan and design their clinical trials by exploring and quantifying potential risks prior to the start of a study. Modeling and simulation allows for the study of a drug's effects in a 'virtual patient population', using mathematical models that incorporate information on physiological systems. Simulations can be used to test assumptions, improve predictability, better characterize risk and identify opportunities to optimize outcomes by observing the effects of different model inputs, thus helping drug developers to improve the planning and design of clinical trials. Physiologically-based pharmacokinetic (PBPK) modeling and simulation integrates prior knowledge and data generated through the prior research and development stages.

The US FDA, European Medicines Agency (EMA), Japanese Pharmaceuticals and Medical Devices Agency, and other global regulatory agencies encourage the use of modeling and simulation. They consider it an important drug development tool, which enhances product and process understanding, with the ultimate goal of ensuring consistent performance once the drug is placed on the market.

Working with Regulators

Working closely with regulators is a key element for successful drug development. Building regulatory advice into a trial program is an effective strategy to mitigate the regulatory risk inherent in product development and improve the likelihood of early product approval.

Regulators in Europe and the United States have created tools to help developers to ensure research and development programs can meet regulatory needs. Requesting scientific advice from the correct regulatory body at the appropriate time has become an essential tool to guide product development and to obtain answers on many aspects of a development program. Requests for advice – and responses – can be multidisciplinary and focus on a broad range of questions, such as product quality, acceptance of novel study designs, pharmacokinetic and pharmacodynamic modeling, biomarkers, and hard versus surrogate endpoints.

The clear message from regulators in both Europe and the United States is that it is

never too early to seek scientific advice. Whether the questions deal with broad issues of study design (for example population, dose selection, statistical aspects) and appropriate indication and study population, or issues of chemistry manufacturing controls (CMC) for a new product class, earlier agency consultation is better.

Human Challenge Models

Human challenge models are designed to generate symptoms and mimic a disease state in an otherwise controlled environment. Testing an investigational compound in such a setting generates the first evidence of efficacy, and in general, similar planning rules apply to all: safety, in-house expertise and necessary equipment are crucial. Viral challenge studies present additional challenges because of the risk of potential contagion and these more challenging and complex phase 1 trials require a facility that is adequately equipped and a team with the required expertise, experience and accountability.

If a challenge study is being considered, the research question must be clearly justified, the proposed methods must be appropriate and provide a meaningful, valid answer and must be as safe as possible with appropriate management of possible risks in place. The selection of study participants must be justified and also safe, with rigorous consent procedures established to ensure full understanding. The clinical site (challenge unit) needs to be adequately equipped and the team experienced.

Protocol and Design

The protocol is a detailed outline of a clinical study that describes the objective(s), design, methodology, statistical considerations and organization of a trial. It should be designed in such a way that it simultaneously ensures the safety of the participants and solid scientific answers. Flaws in the protocol will lead to deviations, violations, amendments and even to missing, invalid or uninterpretable data.

Although a "perfect" protocol may have been created on paper, many study aspects need to be evaluated from a practical point of view. These include: the feasibility of recruiting the exact study population; Investigational Medicinal Product (IMP) preparation steps; the use of sentinel dosing groups; sample-handling processes; decision making process and the frequency and types of assessments. Despite timeline pressures, clear communication on content and operational feasibility is essential if potential issues are to be avoided, and all worst-case scenarios need to be considered.

There is a tendency for early phase clinical trial protocols to become increasingly complex. The focus on gaining as much scientific insight as possible can lead to multiple objectives being embedded into one single design. In these "umbrella" studies some decisions can be made only after analysis of the collected data. To avoid the need for protocol amendments after every decision, adaptive features, such as exact dose levels, the number of cohorts, the regimen for multiple dosing, and assessments to be added or omitted, can be described in a flexible way. As long as the changes follow what is written in the protocol, substantial amendments are not warranted. To meet regulatory requirements, adaptations must be described in detail, clear boundaries must be set and the decision-making process, including rules for stopping, must be clear.

Once the clinical trial protocol has been finalized it must be followed rigorously by the clinical trial team, not only for regulatory reasons, but also to avoid harm to participants and prevent erroneous results and conclusions.

Enrollment and Recruitment

Subject enrollment is a key driver of clinical trial success but remains one of its biggest challenges. Recruitment and retention issues result in trial delays and increased costs and could potentially undermine trial results.

Each clinical trial phase presents specific hurdles in terms of recruitment. Most early phase trials do not offer therapeutic benefit for the subjects and are typically performed in healthy volunteers, for whom the incentive to participate remains mainly a financial one. Conversely, from phase 2 onwards, patient populations are needed. Confronted with disease, study participants tend to be willing to help innovation, but may be deterred by the fear of side effects and of receiving placebo, thereby losing time to get treated.

Early phase studies typically require frequent visits to medical facilities and a number of clinical assessments, so the overall burden and time spent also becomes a decisive factor. In addition, eligibility criteria are more restrictive in early phase, making the search for participants that match the requirements difficult. Identifying factors that affect recruitment, both positively and negatively, simplifying the protocol if possible, to reduce the burden on patients and physicians, and identifying overly restrictive eligibility criteria can all aid recruitment and retention of participants. From a practical point of view, having a realistic recruitment period, using various recruitment tools/activities as well as motivated principal investigators and an experienced site with demonstrated subject access are the critical measures to evaluate to assure recruitment in a timely manner.

Managing a Clinical Trial Facility

The principles of Good Clinical Practice (GCP) ensure the protection of trial participants and the integrity of the data recorded, and all clinical trials must be designed, conducted and reported in accordance with GCP guidelines to be acceptable upon submission for marketing approval.

Any site involved in a clinical trial, including the investigator sites, laboratories, the sponsor's premises, and any contract research organization, may be subject to GCP inspection by regulatory authorities with or without notice. These may be conducted on a routine basis or occur in response to a specific trigger, and can be related to ongoing or completed studies.

During an inspection, an inspector must be able to wholly reconstruct the clinical trial to confirm that all steps have been performed in accordance with the guidelines, that patients' rights and safety were protected at all times, and that all data is reliable.

A solid Quality Management system, consisting of robust standard operating procedures that cover the required measures to maintain high quality standards, should be developed, together with a proactive Quality Control process, which not only checks activities but also aims for continuous improvement. Internal mock audits and inspections are good tools to evaluate whether the quality system is working as intended, and if the team is indeed inspection ready. These types of self-compliance checks provide valuable opportunities for the identification of deficiencies in documentation or processes and lead to a culture of "inspection readiness".

Handling Data

High-quality data are needed in all clinical studies, including exploratory FIH, and should meet the protocol-specified parameters and comply with the protocol requirements. By their nature, FIH and most phase 1 trials are exploratory, without a statistical hypothesis. But despite this, the data need to be relevant, accurate and appropriately analyzed to obtain meaningful results that are useful for future clinical development. There are four main steps in clinical data processing: planning, collection, management and analysis.

When developing the study design/protocol, planning of data at an early stage should consider which measurements to foresee, exactly when, for how long and how frequently. Often, planning is not very targeted in phase 1/FIH protocols because the only supporting information available at this stage is preclinical data and there is no precise statistical endpoint.

Once the study starts, data are collected on an ongoing basis. Any inappropriate methodology and non-adherence to the protocol may adversely affect data reliability and introduce bias. A consequence of the relatively high-risk nature of FIH studies and the absence of therapeutic benefit is an ethical obligation to limit the number of exposed subjects, stressing even more the need for good quality data capture and handling.

Clinical data management is the process of collecting, cleaning, coding and managing subject data in compliance with regulatory standards. The primary objective is to provide good quality data and gather the maximum data for analysis. To meet this objective, best practices (software, standard automatic process, electronic case report forms, electronic data review) should be adopted.

If, at the end of the trial, appropriate methods of analysis are used with the appropriate data, it will be possible to interpret results and come to a conclusion. In the case of FIH studies, the conclusion should enable a decision as to whether to continue or not to the next phase of development and to give initial indications on how to design the next study. Scientifically-sound bridges should therefore be established linking human pharmacology studies to initial exploratory studies and later confirmatory studies.

Planning to Succeed

The ultimate objective of any drug development program is to bring to market a drug product that is safe, and shows positive benefit-risk balance for treatment of the target patient population. The more attention is paid to key areas in the design, planning and execution of the early phase clinical trials, the greater the chances of successfully bringing the product to market.

Ensuring Safety When Using Hazardous Chemistry:
Realizing the Full Potential of Hazard Evaluation and Process Design

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The increasing complexity of New Chemical Entities (NCEs) entering the drug pipeline has fuelled demand for hazardous chemistry techniques which can provide a more efficient route to molecules.

Used to form the basis of synthetic manufacturing processes and access certain functionality within a molecule, these chemistries are helping Active Pharmaceutical Ingredient (API) developers and manufacturers to gain a competitive edge. This is because being able to safely carry out these chemistries at commercial scale provides more options for developing new and more efficient processes.

Hazardous chemistry can offer many benefits to manufacturers including potentially cleaner chemistry, with fewer or no side reactions, or a reduction in the number of synthetic steps. The approach potentially consumes less material, provides easier purification and produces less waste. Additionally, it can generate higher yields of targeted compounds, ultimately leading to a more sustainable environmental footprint for the product.

Ensuring product quality while minimizing the potential environmental impact of hazardous chemistry requires careful consideration, assessment, and planning with expert input.

The Shift towards Hazardous Chemistry

Increased focus on the advantages that hazardous chemistry techniques can bring has led development scientists to explore chemical routes involving simple but energetic molecules. This includes molecules such as ethylene and propylene oxide, diazomethane, epichlorohydrin, hydrazine and hydroxylamine. It has also placed added attention on chemistry involving nitrated species, for example nitroethane and aromatic nitrates, as well as precious metal powder catalysts or pyrophoric catalysts.

While some processes are hazardous due to the energetic nature of a reagent, some reagents that are considered to be innately stable and easy to handle may also react very energetically under certain conditions. Highly toxic reagents also require additional measures and evaluation, such as increased containment or modelling of toxic gas concentrations in the event of unintended release.

The growing trend towards the use of hazardous chemistry has created a need for procedures which allow the potential impact of operating these processes to be reviewed, as well as a careful assessment of the risks involved to be carried out. Assessments need to be conducted and measures put in place to both minimize the risk of injury to personnel and mitigate risks relating to product quality and the impact on the environment as a result of manufacturing.

Health and Safety Executive (HSE) and Regulatory Considerations

Every chemical step introduced into a manufacturing process should be understood and designed with safety in mind.

As the risks associated with hazardous chemistry become more prevalent, higher standards are being enforced. This is achieved

through the introduction of stringent regulations to protect both the health of those working in the industry and the reputations of developers and manufacturers.

Where Major Accidents Hazards (MAHs) are found, manufacturers must be able to demonstrate that a plant or process can operate safely and in accordance with any nationally recognized guidance. If an MAH is associated with the use of certain materials, manufacturers must justify to the authorities why the selected route is still the most appropriate for the desired molecular transformation. An appropriate justification will need to take into consideration the environmental impact and the hazardous nature of the materials used. The outcomes of the hazard evaluation may also be used to demonstrate to the authorities why alternative routes may present greater risks.

Hazard Evaluation: Best Practice Approach

There are several risks associated with any manufacturing process and, as the name suggests, when dealing with hazardous chemistry processes. Therefore, identifying, analyzing and planning to prevent and respond to these potential unique reaction hazards is a necessity.

There are a number of ways in which potential risks can be identified, however every process must be run through a reaction calorimeter. This test identifies potentially dangerous heat and gas outputs caused by reactions. These reaction outputs are then used to define the relevant control strategies for material and reactor cooling additions. For example:

- A vent sizing package (VSP) can be used to assess gas generating reactions and identify emergency venting requirements during scale up, including emergency cooling and venting requirements, as well as emergency shutdown systems and response procedures.
- Taking samples of the reaction mixture throughout the testing process; then assessing the sample using differential scanning calorimetry (DSC), allows processes to be screened for thermal activity and decomposition temperatures.
- Accelerating rate calorimetry (ARC) can be conducted to identify potential thermal onset temperatures for runaway reactions and subsequent pressure rises.
- Minimum Ignition Energy (MIE) identification, 20 liter sphere tests for dust explosion classification and electrostatic charge relaxation identification.

Application of Hazard Evaluation to Process Design

Due to the specialized nature of hazardous chemistry, well thought out integration of hazard evaluation, engineering, chemistry and analytical expertise are required, as well as knowledge of how the scale up process and larger volumes could impact operations and resulting safety requirements. To ensure an optimum process a multidisciplinary team, who are experts in their field, is required to review the process. This team should comprise of process engineers, hazard evaluation scientists, production and plant engineering, and development chemists.

The information gathered during the hazard evaluation will then be assessed by this team and the insight gained during this assessment can then be used to advise the design of the manufacturing plant.

Where MAHs are identified as having the potential to effect an individual's safety or the environment, a more detailed risk assessment will then follow. This will include a Layer of Protection Analysis (LOPA) or a Quantified Risk Assessment (QRA). This then needs to be provided to the team working on the project in addition to the assessment and definition of the Safety Integrity Level (SIL) of any required instrumentation.

Where hazards are identified, the engineer may propose changes which aim to reduce the consequences of the hazard. However, this may require further investigation and approval by the chemist. Ultimately, the output of the safety review could mean additional investigation into the chemistry is necessary as it may need to be modified in order to be operated safety at scale, for example, it may be necessary to adopt a different order of operation or alternative reagents.

By putting in place a cross-disciplined team, chemists and engineers can work together to eliminate or reduce the consequences of identified hazards. This in turn helps to ensure more successful and safe outcomes for their manufacturing processes, as well as comprehensively ensure that the chosen process is suitable for scale up.

Future-Proofing

Testing processes prior to manufacture can significantly reduce the potential for hazards. Similarly, identifying hazards early in the development phase can bring considerable efficiencies to overall development programs. Post-validation or post registration, it is generally time consuming and expensive to change the established process. Early identification can also influence the choice of reagents and conditions to eliminate or, at least minimize, the consequences.

It is essential that commercial manufacture is taken into consideration from the outset. Processes also need to be safe and scalable to future-proof the supply of a product and ensure the processes are both viable and safe on a larger scale.

Advances in technologies, such as continuous processing, are helping to make hazardous chemistry more accessible. With such approaches, the risks associated with the processing of hazardous materials are reduced as a result of a decrease in the inventory of hazardous materials.

This type of manufacturing is beneficial for the right products as it is able to limit impact if failures allow materials to reach onset temperatures. Furthermore, it ensures hazardous by-products can be effectively quenched at low volumes. While the initial investment may be comparable to a new batch reactor, there are several risk reduction benefits to be gained, as well as cost savings linked to the maintenance of safety systems and in supporting regulatory audits.

Summary

Hazardous chemistry may present the most economically viable and environmentally responsible route to a particular molecule. It brings with it several advantages, including more direct and cost-effective processes that result in the production of better yields. However, it also brings new risks that must be managed with the support of dedicated chemistry and engineering expertise. Evaluations need to be undertaken to establish a complete understanding of all hazards associated with a process, with measures being put in place to eliminate or minimize the impact of these on both human safety and the environment.

Hazard evaluation is a highly specialized field meaning it is vital to put a highly competent team in place in order to ensure more successful and safe outcomes for manufacturing processes.

Many pharmaceutical manufacturers lack the necessary expertise in- house. Subsequently, they are turning to contract partners that can bring specialist knowledge and broad experience of manufacturing complex products. These providers are also highly experienced at putting the right teams in place to offer precise and efficient control of process conditions.

While finding the right manufacturing partner will require careful consideration and thorough evaluation of credentials and prior safety records, the need for strong hazard evaluations and health and safety protocols will continue to grow as more and more complex APIs enter development.

Sam Brogan, PhD, is Lab Project Manager of the R&D department at Sterling Pharma Solutions and is responsible for leading a team of development chemists and senior scientists working across several process development projects. Sam joined the Sterling team in 2012 as a development chemist and assumed responsibility as the technical lead for the introduction of several hazardous processes to plant. In her current role Sam works with her team to perform development work to gain process understanding and make the process cheaper, more efficient, more robust and support the transfer to manufacture.

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Editor's Choice

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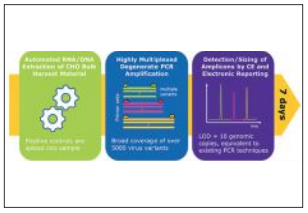

The BioReliance® Blazar™ Platform meets the need to accelerate detection of adventitious viral contamination. This rapid molecular platform/degenerate PCR approach detects panel specific targeted viruses and related, but unknown viral contaminants and benefits the industry in several ways. It accelerates the broad and sensitive detection of adventitious viruses by replacing biological growth-based systems with a molecular approach. It provides manufacturers with accurate and highly sensitive viral detection in just days. Combining the breadth of detection of NGS with the speed and sensitivity of PCR. The Blazar™ Platform relies on degenerate PCR primers enabling coverage of beyond 5000 viral variants and will drive transformation of biosafety testing, particularly since the current method was developed in 1964. The Blazar™ platform enables biopharma to bring therapies to market faster.

https://www.emdmillipore.com/US/en/services/biopharmaceutical-manufacturing/Rapid-Molecular-Testing/Jk2b.qB.e1wAAAFwEPEXejXl,nav

Biotech Innovation

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http://files.aievolution.com/prd/ipx2001/abstracts/abs_1224/accuflux-filter-integrity-tester.pdf

Best Technologies Innovation

PolarDry Electrostatic Systems

Fluid Air

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www.fluidairinc.com/index.html

Efficiency Champion

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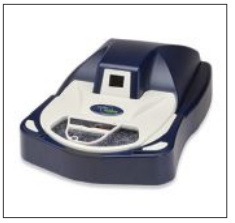
SUEZ - Sievers



The new BET Platform, along with Sievers TOC Analyzers platform, automates endotoxin assay setup through precise microfluidic liquid handling and embedded endotoxin standards. It maintains full compliance with the harmonized pharmacopoeias with embedded standards derived from the reference standard endotoxin produced by the USP along with FDA licensed limulus amoebocyte lysate. The Eclipse enhances the product development lifecycle by simplifying an otherwise antiquated and cumbersome benchtop assay and decreasing demand on natural resources. Using the Eclipse, manufacturers can gain operational efficiency by reducing pipetting steps by up to 89%, reducing analyst time by up to 85% and reducing the use of horseshoe crab lysate by up to 90%. The Eclipse enables fully compliant, 21-sample assay setup in as little as 9 minutes.

www.suezwatertechnologies.com/products/analyzers-instruments/sievers-eclipse

HORIZON LINES

A Quarterly Review of NDAs – April-June 2020

Sunny Christian, MSRA, Neelam Sharma, MS and Hemant N. Joshi, PhD, MBA[#]

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This quarterly review on New Drug Applications contains data for applications approved for the first time during April-June of 2020, which includes New Molecular Entities (NMEs) and new biologics. A total of 43 applications were approved by FDA during these three months.

Following are the percentages of various dosage forms in this quarter-18.6% tablets, 7% oral liquids, 32.6 % injectables, 14% capsules, 7% gas inhalation, 4.7% topical, and 16.3% others. Other dosage forms include pyelocaliceal powder, sublingual film, nasal spray and vaginal formulations. Based on the submission classification, the NDAs can be divided as follows: new molecular entity (Type 1) – 30.2%, new active ingredient (Type 2) – 2.3%, new dosage form (Type 3) – 18.6%, new combination (Type 4) – 4.6%, new formulation or manufacturer (Type 5) – 16.3%, new indication consolidated with original NDA – 2.3%, new indication, non-consolidated with original NDA – 2.3%, Biological License Application (BLA) – 16.3% and others – 7%.

During this quarter, FDA approved Seattle Genetics' TUKYSA (Tucatinib) and Desiphera Pharms' QINLOCK (Ripretinib) applications under the Real-Time Oncology Review (RTOR) pilot program. The Oncology Center of Excellence RTOR pilot program is a more streamlined and efficient way to review applications. This program focuses on early submission of data that are the most relevant to assessing the product's safety and effectiveness. The FDA will have the flexibility to review the data before the information is formally submitted to FDA. This early engagement may improve the quality of the NDA submission and FDA's evaluation of the application. Acceptance into the RTOR pilot program does not guarantee or influence approvability of the application.

Evoke Pharma obtained FDA approval for GIMOTI (metoclopramide) nasal spray. GIMOTI is the first and only nasally administered product for acute and recurrent diabetic gastroparesis. Gastroparesis is a disease that blocks or slows the movement of the contents of the stomach to the small intestine. Oral drug administration is often compromised. This novel nasal formulation provides an alternative mean of delivering metoclopramide in patients with delayed gastric emptying and/or frequent vomiting.

In May 2020, FDA approved ORIAHNN™ (Elagolix, estradiol, and norethindrone acetate capsules; Elagolix capsules). It is the first non-surgical, oral medication option for the management of heavy menstrual bleeding associated with uterine fibroids in pre-menopausal women. It is a non-invasive treatment that not only reduces the amount of bleeding but may also help another side effect of fibroids in some women: iron-deficiency anemia.

Two products received the orphan drug status in this period. They are – Ferriprox, Deferiprone tablets by Chiesi and Tazverik, Tazemetostat HBr by Epizyme, Inc.

PDA
Parenteral Drug Association

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Approval Date	Drug Name	Active Ingredients	Submission Classification	Company	Dosage form/ route	Comments
04/10/20	Koselugo	Selumetinib sulfate	Type 1	Capsule; oral	AstraZeneca	Treatment of pediatric patients two years of age and older with neurofibromatosis type 1.
04/13/20	Dolutegravir	Lamivudine; tenofovir disoproxil fumarate	Type 4	Tablet; oral	Celltrion Inc.	Reviewed under the President's Emergency Plan for AIDS Relief.
04/15/20	Jelmyto	Mitomycin	Type 5	Powder; pyelocalyceal	UroGen Pharma	Novel formulation for the treatment of low-grade upper tract urothelial cancer.
04/17/20	Emerphed	Ephedrine sulfate	Type 5	Solution; intravenous	Nexus Pharmaceuticals	A ready-to-use formulation of ephedrine.
04/17/20	Tukysa	Tucatinib	Type 1	Tablet; oral	Seattle Genetics	Approval under the Real-Time Oncology Review (RTOR) pilot program.
04/17/20	Pemazyre	Pemigatinib	Type 1	Tablet; oral	Incyte Corp.	An accelerated approval based on overall response rate and duration of response.
04/22/20	Trodelvy	Sacituzumab govitecan-hziy	BLA	Injectable; injection	Immunomedics Inc...	First Antibody-Drug Conjugate approved specifically for metastatic TNBC.
04/24/20	Ongentys	Opicapone	Type 1	Capsule; oral	Neurocrine	Once-daily oral add-on treatment to levodopa/ carbidopa in Parkinson's disease.
04/28/20	Bafiertam	Monomethyl fumarate	Type 2	Capsule, delayed release; oral	Banner Life Sciences	A novel fumarate for the treatment of relapsing multiple sclerosis.
04/29/20	Milprosa	Progesterone	Type 3	System; vaginal	Ferring Pharmaceuticals.	Approved as a new dosage form.
05/01/20	Fensolvi kit	Leuprolide acetate	Type 10	Powder; subcutaneous	Tolmar	Treatment of pediatric patients with central precocious puberty.
05/01/20	Darzalex faspro	Daratumumab; hyaluronidase-fihj	BLA	Injectable; injection	Janssen Biotech	Approved in four regimens across five indications in multiple myeloma.
05/05/20	Elyxyb	Celecoxib	Type 3	Solution; oral	Dr. Reddy's	Acute treatment of migraine with or without aura in adults.
05/06/20	Tabrecta	Capmatinib hydrochloride	Type 1	Tablet; oral	Novartis	An accelerated approval based on overall response rate and duration of response.
05/08/20	Retevmo	Selpercatinib	Type 1	Capsule; oral	Loxo Oncology Inc.	First therapy for patients with advanced RET-driven lung and thyroid cancers.
05/14/20	Pemetrexed for injection	Pemetrexed	Type 5	Injectable; injection	Dr. Reddy's	Applied under 505(b)(2) regulatory pathway.
05/15/20	Qinlock	Ripretinib	Type 1	Tablet; oral	Deciphera Pharmceuticals	Approval under the Real-Time Oncology Review (RTOR) pilot program.
05/19/20	Ferriprox	Deferiprone	Type 5	Tablet; oral	Chiesi	It has orphan drug designation.
05/19/20	Impeklo	Clobetasol propionate	Type 5	Lotion; topical	Mylan	Applied under 505(b)(2) regulatory pathway.
05/20/20	Cerianna	Fluoroestradiol f-18	Type 1	Solution; intravenous	Zionexa	A PET imaging agent for use in patients with recurrent or metastatic breast cancer.
05/21/20	Kynmobi	Apomorphine hydrochloride	Type 3	Film; sublingual	Sunovion Pharmaceuticals Inc.	A novel sublingual film for the treatment of Parkinson's disease OFF episodes.
05/22/20	Phexxi	Citric acid; lactic acid; potassium bitartrate	Type 3 and Type 4	Gel; vaginal	Evofem Inc.	A non-hormonal prescription gel for the prevention of pregnancy.
05/26/20	Vesicare LS	Solifenacin succinate	Type 3	Suspension; oral	Astellas	For treatment of neurogenic detrusor over-activity.
05/26/20	Artesunate	Artesunate	Type 1	Powder; intravenous	Amivas	An antimalarial indicated for the initial treatment of severe malaria.

Approval Date	Drug Name	Active Ingredients	Submission Classification	Company	Dosage form/ route	Comments
05/28/20	Tauvid	Flortaucipir f-18	Type 1	Solution; intravenous	Avid Radiopharmaceuticals, Inc.	A PET imaging agent for use in patients being evaluated for Alzheimer's disease.
05/28/20	Zilxi	Minocycline hydrochloride	Type 5	Aerosol, foam; topical	Foamix	Topical tetracycline for the treatment of inflammatory lesions of rosacea in adults.
05/29/20	Artesunate	Artesunate	Type 1	Injectable; injection	La Jolla Pharmaceutical Company	An antimalarial indicated for the initial treatment of severe malaria.
05/29/20	Oriahnn (copackaged)	Elagolix sodium, stradiol, norethindrone acetate; elagolix sodium	Type 4	Capsule; oral	AbbVie Inc.	First oral non-surgical option for the management of heavy menstrual bleeding.
06/02/20	Oxygen, USP	Oxygen	-	Gas; inhalation	Air Liquide Canada Inc.	Certified as a designated medical gas.
06/10/20	Nyvepria	Pegfilgrastim-apgf	BLA	Injectable; injection	Hospira Inc.	Pegylated growth colony-stimulating factor biosimilar to Neulasta.
06/11/20	Semglee	Insulin glargine	BLA	Injectable; injection	Mylan	Long-acting human insulin analog for type 1 and type 2 diabetes mellitus.
06/11/20	Uplizna	Inebilizumab-cdon	BLA	Injectable; injection	Viela Bio	Treatment of Neuromyelitis Optica Spectrum Disorder.
06/12/20	Tivicay PD	Dolutegravir sodium	Type 3	Tablet, for suspension; oral	ViiV Healthcare	For the treatment of HIV-1 infection.
06/15/20	Zepzelca	Lurbinectedin	Type 1	Powder; intravenous	Jazz Pharmaceuticals	An accelerated approval based on overall response rate and duration of response.
06/15/20	Lyumjev	Insulin lispro-aabc	BLA	Injectable; injection	Eli Lilly and Co.	Rapid-acting human insulin analog for type 1 and type 2 diabetes mellitus.
06/18/20	Tazverik	Tazemetostat hydrobromide	Type 9	Tablet; oral	Epizyme Inc.	Orphan drug designation.
06/19/20	Gimoti	Metoclopramide hydrochloride	Type 3 and Type 4	Spray, metered; nasal	Evoke Pharma, Inc..	First and only nasal product for acute and recurrent diabetic gastroparesis.
06/25/20	Fintepla	Fenfluramine hydrochloride	Type 3	Solution; oral	Zogenix Inc.	An amphetamine derivative for the treatment of seizures associated with Dravet syndrome.
06/26/20	Mycapssa	Octreotide acetate	Type 5	Capsule, delayed release; oral	Chiasma	First and only oral somatostatin analog approved by the FDA.
06/27/20	Helium, USP	Helium	-	Gas; inhalation	Westair Gases & Equipment Inc.	Certified as a designated medical gas.
06/29/20	Nitrogen, NF	Nitrogen	-	Gas; inhalation	Air Liquide Canada Inc.	Certified as a designated medical gas.
06/29/20	Phesgo	Pertuzumab; trastuzumab; hyaluronidase-zzxf	BLA	Injectable; subcutaneous	Genentech Inc.	A fixed-dose combination for the treatment of early and metastatic HER2-positive breast cancer.
06/30/20	Dojolvi	Triheptanoin	Type 1	Liquid; oral	Ultragenyx Pharmaceutical Inc.	Source of calories and fatty acids for the treatment of Long-Chain Fatty Acid Oxidation Disorders.

Type 1 = New Molecular Entity, Type 2 - New Active Ingredient, Type 3 - New Dosage Form, Type 4 - New Combination, Type 5 - New Formulation or New Manufacturer, Type 9 - New Indication, Consolidated with original NDA, Type 10 - New Indication, non-consolidated with original NDA, and BLA - Biologics License Application

JanOne Completes Formulation of JAN101 in Preparation for GMP Manufacturing Batch

JanOne together with its manufacturing partner, has successfully completed the formulation of JAN101, its potential treatment for Peripheral Artery Disease (PAD) expected to soon be in Phase 2b trials. In addition, JAN101 is planned for use to treat COVID-19 vascular complications pending approval of the IND submission, expected to be completed in late August 2020.

JAN101 is one of the few promising treatments for vascular conditions using sodium nitrite that showed success in Phase 1 and Phase 2a trials for improving blood flow and vascular function. The company is preparing its IND packages for FDA submission for continued development as a treatment of PAD and to extend JAN101 to potentially mitigate severe organ and tissue damage caused by COVID-19. The successful formulation of JAN101 will allow the company to begin its engineering run and GMP manufacturing for multiple trials expected to begin in early 2021.

"Working with our manufacturing partner, we have been able to successfully produce JAN101, our sustained release formulation and expect our engineering batch to begin immediately," said Dr. Tony Giordano, chief scientific officer at JanOne. "We believe we will have the initial GMP batch of 250,000 doses by mid-September 2020. This will provide us with enough tablets to carryout our proposed Phase 2b PAD trials and the COVID-19 treatment study IND, which we are confident will gain approval."

The company will now focus on commercial production capability of JAN101 and is currently negotiating to purchase 1,000 kilos of sodium nitrite from a multinational biopharmaceutical company to support GMP manufacturing batches of more than 20 million doses of JAN101.

Avacta Appoints Therapeutics Chief Development Officer

Avacta Group announced the appointment of Neil Bell as Chief Development Officer of Avacta Life Sciences with immediate effect. Neil will be responsible for late stage pre-clinical and early clinical development of Avacta's pipeline of pre|CISION pro-drugs and Affimer immunotherapies.

Bell has over 30 years' experience in the drug development industry, having held senior positions in global pharmaceutical companies and biotechs. The early part of his career was spent in clinical development at Eisai and Pfizer before becoming Therapeutic Area Head for Gastroenterology and Neurology at Ipsen. In each of these roles he led numerous Phase I to III clinical studies, gaining significant experience across all facets of drug development; from strategy to pre-clinical development, manufacturing and regulatory, to clinical study design and implementation.

In his role as Head of Global Clinical Operations for Teva Pharmaceuticals, Bell led an international team responsible for the delivery of clinical programs in neurology, autoimmune and oncology therapeutic areas. During this period, he contributed to the development of Copaxone achieving leadership in the treatment for multiple sclerosis globally, as well as successfully introducing Azilect to global markets.

Following this period at Teva, Bell joined Daichi-Sankyo as Head of Clinical Operations where he led the clinical operations team through early and late stage development activities across cardiovascular, pain and oncology, and was responsible for building an effective drug development organization in Europe serving the global clinical programs and leading to the successful global approval of Edoxaban.

Most recently, Bell held the role of Senior Vice President, Head of Global Clinical Operations at Autolus, a UK cell and gene therapy company backed by Syncona, which listed in the US in 2018; a process in which Neil played a key role. At Autolus Neil was responsible for building a fully functional global clinical operations team delivering Phase I/II clinical studies across the UK, Europe and US in acute lymphoblastic leukemia, multiple myeloma, B-cell lymphoma, and T-cell lymphoma, and implemented the first commercially sponsored CAR-T study in the UK.

"I am absolutely delighted that Neil is joining Avacta as Chief Development Officer to build and lead the development team to take a pipeline of innovative cancer therapies into the clinic over the next few years; therapies that have the potential to significantly enhance cancer patients' lives," Dr. Alastair Smith, Chief Executive of Avacta Group said. "Not only does Neil have tremendous drug development and operational experience, but he also brings significant strategic insight and will be a key member of the senior leadership team driving the Group's drug development and corporate strategy for the therapeutic business. I am very much looking forward to working with Neil as we continue to transition the business to a clinical stage biotech with multiple clinical programs in the UK, Europe and the US, building upon the world-class proprietary platforms and assets that we have developed in-house and with partners over the past few years.

"I am delighted to join the therapeutics team at Avacta Life Sciences at such an exciting time in its growth trajectory and where I believe the Company has significant opportunity to build a successful and agile clinical stage biopharmaceutical organization with the capability to maximize its early development oncology assets for the ultimate benefit of patients. I very much look forward to working closely with Alastair and the therapeutics senior leadership team to establish a leading position for Avacta Life Sciences as a focused immunotherapy oncology company," Neil Bell, Chief Development Officer of Avacta Group said.

Emmes Announces its Role in Phase 1 COVID-19 Vaccine Trial

Emmes announced that it provided the data and statistical analysis support for the Phase 1 clinical trial of the investigational COVID-19 vaccine mRNA-1273. Three Emmes employees were co-authors on the

Preliminary Report about the clinical trial, "An mRNA Vaccine against SARS-CoV-2," published in the New England Journal of Medicine on July 14.

The employees are Jim Albert, lead project manager; Dr. Mat Makowski, senior biostatistician; and Kaitlyn Cross, senior biostatistician.

"Emmes launched the trial's electronic data collection system in about a month. Our team was driven to do everything we could to contribute to this critical human health challenge," Albert said.

The vaccine was co-developed by researchers at the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, and at Moderna, which was involved in trial design discussions and provided the vaccine candidate. Emmes served as the statistical and data collection and coordination center, developed the statistical analysis plan, and performed the analysis.

The Phase 1 trial began in March 2020 to determine the safety of the mRNA-1273 vaccine and its ability to induce an immune response. The open-label trial included 45 healthy adults, ages 18 to 55, who received two vaccinations, 28 days apart. The vaccine resulted in anti-SARS-COV-2 immune responses in all participants, and there were no trial-limiting safety concerns.

"It has been a privilege to collaborate with Moderna and with NIAID in developing a vaccine for COVID-19," said Dr. Anne Lindblad, Emmes president and chief executive officer. "The successful Phase 1 trial has paved the way for the subsequent clinical trials."

The company has supported research for infectious diseases such as H1N1 influenza, SARS, Ebola and Zika, among others, and now for COVID-19.

This project has been funded in whole or in part with federal funds from the National Institute of Allergy and Infectious Diseases, National Institutes of Health, Department of Health and Human Services, under Contract No. HHSN272201500002C.

ANA Therapeutics, Quotient Sciences Announce Partnership to Manufacture Niclosamide

ANA Therapeutics and Quotient Sciences announced a partnership to support the manufacturing of ANA Therapeutics' drug candidate, ANA001 (niclosamide capsules), which they are developing as a potential treatment for COVID-19. As part of the collaboration, Quotient will scale up the capsule formulation, characterize and optimize the manufacturing process and ensure continuity of drug product through clinical trials.

Laboratory experiments have shown niclosamide stops SARS-CoV-2 (the virus that causes COVID-19) from replicating, making it a promising candidate for reducing the spread of COVID-19. Niclosamide was previously approved by the FDA as a treatment for tapeworm and although not currently marketed in the U.S., it is on the World Health Organization's List of Essential Medicines and has been used for decades to safely treat millions of people around the world.

"We have selected Quotient Sciences as our development and manufacturing partner and our plan is simple," said Andrew Bartynski, COO, ANA Therapeutics. "Niclosamide has the potential to be an effective antiviral agent to combat COVID-19, and our top goal is to complete a clinical trial to determine its efficacy in treating patients with COVID-19. Quotient's speed and agility will play a key role in reaching that important milestone."

"We are proud to partner with ANA Therapeutics in their pursuit of a treatment to fight this coronavirus pandemic. Our experience and flexible manufacturing approaches will enable ANA Therapeutics to initiate clinical testing in an accelerated timeframe," Mark Egerton, Ph.D., CEO of Quotient Sciences, said.

Under the scope of the agreement, ANA Therapeutics will access Quotient's formulation and manufacturing expertise to develop and rapidly supply drug product for pivotal clinical trials in Q3 2020. The program will be conducted at Quotient's facility in Garnet Valley, Pennsylvania.

Multiple Headlands Research Sites Selected for AstraZeneca's Phase III COVID-19 Vaccine Trial

Headlands Research announced its research centers have been selected to participate in AstraZeneca's upcoming Phase III COVID-19 vaccine trial. Headlands has built a position in the vaccine and infectious disease space, successfully conducting over 250 vaccine, prophylaxis and treatment trials to date across its North American sites.

Recruitment efforts for the AstraZeneca vaccine are actively underway at four of Headlands' research sites, including: Atlanta, GA; McAllen, TX; Lake Charles, LA; and Palm Beach, FL. Headlands employs a diversity of traditional and non-traditional recruiting sources for its COVID-19 vaccine and treatment trials, with a strong focus on ensuring the inclusion of a wide array of ethnic and age groups.

"A vaccine for COVID-19 is crucial to overcome the current pandemic, and we appreciate the opportunity to work with AstraZeneca on this important Phase III trial," said Mark Blumling, CEO of Headlands Research.

HTG Molecular Announces Commercialization, Distribution Agreement with QIAGEN

HTG Molecular Diagnostics announced the signing of a Commercialization and Distribution Agreement with QIAGEN Manchester Limited, a wholly owned subsidiary of QIAGEN.

The Agreement allows HTG to engage directly with biopharma customers for CDx development programs including assay development, clinical trial oversight and global regulatory submissions, with potential CDx assays developed leveraging either an Illumina or a Thermo Fisher Scientific NGS platform. In the event a

CDx assay is required, the agreement provides HTG's customers global distribution and commercialization options with QIAGEN, a proven world-class molecular diagnostics leader.

"Our biopharma customers want the ability to develop new biomarkers with our HTG EdgeSeq technology, along with the ability to distribute them globally. This new agreement is designed to allow them to do just that," said Byron Lawson, Senior Vice President and Chief Commercial Officer. "Ultimately, we can now provide our customers with the confidence that they will be able to use our HTG EdgeSeq technology and capabilities, while leveraging the proven commercial expertise and distribution scale of QIAGEN."

"This new agreement preserves the original value we saw when we initially collaborated with QIAGEN in 2016; HTG EdgeSeq technology, leveraging either an Illumina or Thermo Fisher Scientific sequencer, with global commercialization and distribution options offered by QIAGEN, one of the largest molecular diagnostic companies in the industry. We are extremely pleased we were able to renew our partnership with QIAGEN and look forward to contracting new CDx programs to deliver on our mission to advance precision medicine," John Lubniewski, President and Chief Executive Officer, said.

Ajinomoto Bio-Pharma Services Expands Small Molecule Manufacturing Capabilities at India Facility

Ajinomoto Bio-Pharma Services has announced an expansion of small molecule manufacturing capabilities with the addition of a new production facility in Visakhapatnam, India. Construction of the 8,500 square meter facility began at the end of July 2020 and is expected to be completed mid-2022.

To meet the current and future needs of customers, the new small molecule manufacturing facility doubles the production capacity at the site to 310 m3 for active pharmaceutical ingredients (API) and intermediates and has dedicated equipment to manage OEB 4 high potency ingredients. Further, the site has completed renovations on existing laboratory space to support additional R&D activities. It is estimated that the expansion will create at least 60 new jobs at the site.

The FDA approved Ajinomoto Bio-Pharma Services India manufacturing site, which was designed, constructed and is managed based on the Aji Bio-Pharma Belgian sites' GMP operating standards and quality systems, has successfully supported a number of the world's leading biopharmaceutical companies since its formation in 2011 and continues to win awards for sustainability and quality standards.

"We are very excited to be investing in this additional production capacity to continue delivering high quality, cost-effective small molecule manufacturing services for our customers," said K.V.V. Raju, Head of Site Operations and CEO, Ajinomoto Bio-Pharma India Pvt. Ltd. "This expansion exemplifies our commitment to our vision statement of being a leading, trusted, innovative partner to our clients and our people."

"The increased manufacturing capacity at Aji Bio-Pharma India offers a significant advantage for our small molecule customers, who now have a variety of options to meet their manufacturing needs," said Peter Stuyck, Sr. Vice President and Head of European Operations, Ajinomoto Bio-Pharma Services. "This expansion optimizes capacity across all locations and further enhances Aji Bio-Pharma's commitment in being a leading global and quality-driven CDMO with comprehensive service offerings."

BioStem Life Sciences Signs Manufacturing Agreement for Amniotic Membrane Allograft Platform

BioStem Technologies announced its subsidiary, Blue Tech Industries (doing business as BioStem Life Sciences), has signed a Master Service Agreement with a new customer to manufacture the customer's amniotic membrane platform for the next two years, in a deal estimated to be worth up to $2.4 million to BioStem. The agreement also allows the companies to initiate additional projects in the future.

"We are excited that this new customer has chosen BioStem Life Sciences to manufacture their amniotic tissue allograft products. The decision to invest further in our facility and expansion of services is solidifying the sustainable business model for the Company in the Contract Manufacturing sector," said Andrew Van Vurst, Chief Operations Officer for BioStem Technologies.

NanoImaging Services Opens West Coast Facility

NanoImaging Services announced the opening of a new facility close to their San Diego headquarters. It will be the largest private facility for cryoEM data collection globally and will serve both its national and international clients.

Designed to be a data collection farm, this new facility will host up to four Thermo Scientific Krios Cryo-TEM microscopes, which will all be equipped with the latest Gatan K3 detector and Gatan Quantum energy filter, plus a state-of-the-art Thermo Scientific Glacios Cryo-TEM microscope for grid screening. An ultra-high speed, dedicated data line will connect it directly to the San Diego headquarters and Boston client center, so users can work directly with the NIS microscopists and view images in real-time with the company's remote image viewer. The first Thermo Scientific Krios at the new facility has already been commissioned and is heavily booked through the end of 2020. A new, formal agreement between NIS and Thermo Scientific will allow the company to add more capacity with minimal lead time.

"Together, the coupling of this new infrastructure with industry-leading flexible service models, continues to break down many of the barriers to entry for industry groups of all sizes to participate in the "resolution revolution." said Clint Potter, founder and CEO of NanoImaging Services. "The new facility supports the continued growth of our company and underlines our commitment to advancing cryoEM technology and access. We are excited to leverage our

increased microscope capacity to serve new and existing customers around the world, as well as help more researchers develop their own cryoEM project pipelines."

The rapid development in cryoEM technology has established the technique as an essential tool for application in structure-based drug discovery, but also highlighted its relevance throughout the drug development pipeline in areas such as antibody development, virus and vaccine studies, characterization of drug delivery vehicles and biopharmaceutical QA/QC. Working closely with their biotechnology and pharmaceutical clients, the NanoImaging Services teams enable valuable access to TEM and cryoTEM methods alongside their extensive expertise and technical support for improved structural analysis, in a time- and cost-effective manner.

Since acquiring its first Thermo Scientific Krios Cryo-TEM microscope in 2018, NanoImaging Services has grown rapidly. Its cryoEM and negative stain workflows are used by leading pharmaceutical, biotechnology and diagnostics companies, as well as by academic researchers worldwide.

Cobra Biologics Completes Production of Master Cell Banks for Epilepsy Gene Therapy Candidate

Cobra Biologics CombiGene announced Cobra has successfully produced master cell banks for the three plasmids used as starting material for CombiGene's gene therapy CG01.

The three master cell banks have been developed according to Good Manufacturing Practice (GMP). GMP-compliant cell bank production assures stable and uniform populations of cells are preserved as starting material for all future batches of the three plasmids and a sufficient supply of material is readily available for the life of the product. Ensuring the quality and characteristics of the plasmids are identical at each individual production time, the master cell banks can thus be used each time CombiGene produces new plasmids for production of CG01 whether that be for future clinical studies or commercial production.

This follows the recent milestone announcement that Cobra had successfully produced and supplied all three of the plasmids that form the starting material and are key components in the production of CombiGene's gene therapy vector, CG01. This gene therapy vector is tasked with "transporting" CG01's active substances NPY and Y2 into the patient's brain tissue.

"The fact that we now have the three master cell banks in place means that all further production of plasmids, used in the manufacturing of CG01, for the final preclinical and clinical studies as well as future treatments, take place from a stable and safe basis," Karin Agerman, Chief Research and Development Officer, CombiGene said.

"The generation of DNA cell banks is the vital first step in the product commercialisation journey. Cobra is excited to continue that journey with CombiGene and their CG01 epilepsy gene therapy drug candidate," Peter Coleman, Chief Executive, Cobra Biologics said.

Catalent Gene Therapy Facility Receives FDA Approval as Manufacturing Site

Catalent announced that it has been approved by the U.S. Food and Drug Administration (FDA) to produce commercial drug substance intermediate for AveXis' spinal muscular atrophy (SMA) gene therapy at its manufacturing facility located in Harmans, Maryland.

The approval comes after an FDA inspection of the Harmans commercial-scale gene therapy manufacturing center in June 2020. Since Catalent's partnership with AveXis, a Novartis company, was announced in July 2019, dedicated suite space has been prepared at the Harmans facility for the commercial manufacture of this adeno-associated virus (AAV) gene therapy.

"This is a significant milestone for Catalent and the gene therapy industry as a whole. Catalent is proud to be the first contract development and manufacturing organization to be approved for commercial gene therapy production," said Manja Boerman, Ph.D., President of Catalent Cell & Gene Therapy. "This approval allows us to leverage our now-licensed, state-of-the-art GMP commercial manufacturing facility, and our deep AAV expertise, to support AveXis as it delivers a life-changing treatment for patients."

"Given the complexity and length of time required to make gene therapies, manufacturing is critically important," said Dannielle Appelhans, Chief Technical Officer for AveXis. "This approval further complements our internal manufacturing capacity and, over time, will allow us to increase supply to meet growing patient needs."

Catalent's Harmans commercial manufacturing facility is equipped with single-use technology, and houses over 200,000 square feet of late-stage clinical and commercial-stage gene therapy production. The facility is one of Catalent's five gene therapy facilities in Maryland providing clinical through commercial scale services, and houses multiple CGMP manufacturing suites, including fill/finish, central services and testing laboratories, warehousing, and supply chain capabilities.

Beroni Signs Agreement with Genscript Biotech to Study, Develop Nanobody Solution for COVID-19

Beroni Group has an agreement with GenScript Biotech to conduct antibody characterization and optimization through humanization and affinity maturation with the objective of increasing the antibody affinity to target the antigen by five to ten-fold.

Genscript will render the services based on 3 phases: (1) Perform pseudovirus neutralization assay with candidate antibody (2) Production and characterization of humanized antibodies and (3) Using PML (Precise Mutagenesis Library) and FASEBA (Fast Screening

for Expression, Biophysical-Properties and Affinity) to carry out affinity maturation and purification of the antibodies. The process is expected to take 15-18 weeks.

Nanobody-based technology will not only have the potential to rapidly deliver an effective and safe testing and treatment solution for COVID-19, but also provide an economic, scalable, high-yield and large-scale production capability.

"We are pleased to be able to work with Genscript, one of the world's largest molecular biology CDMO (Contract Development and Manufacturing Organization) companies, to use their leading CDMO platform to further advance our study into the use of nanobodies for treating COVID-19 patients. Nanobody, which has more natural advantages than traditional antibody, is more suitable as a neutralizing antibody to treat coronavirus patients. Nanobody treatment is fast emerging as an effective antibody drug in the market. We will do our utmost best to accelerate our clinical study so that we can produce a timely, safe and effective medical solution to help stop the global spread of this highly infectious disease," Jacky Zhang, Chairman and CEO of Beroni Group, said.

"COVID-19 is still on the rise globally. During this period, we are pleased to collaborate with Beroni Group to use our CDMO platform to facilitate research on nanobodies for the treatment of COVID-19 patients. It is believed that with our joint efforts, this technology can appear in the market as soon as possible for the benefit of patients," Brian Min, CEO of GenScript ProBio, said.

Devana Solutions, BEKHealth Combine Site Performance Metrics with Protocol-to-Patient Matching

BEKHealth and Devana Solutions have finalized an agreement to integrate their platforms. The two companies, makers of the technology solutions targeting clinical research organizations are confident their combined technology will assist research sites, Sponsors and CROs seeking to align the right study with the right sites with the right patients.

"The combination of a site's historical performance data with a highly precise feasibility AI solution which can cover >90% of study criteria increases the reliability of site selection exponentially", said Jason Baumgartner, CEO of BEKHealth. "Historical performance is extremely valuable in predicting performance yet alone can lead to disparities and missed opportunities for customers to uncover new patient populations. With Devana's IGNITE platform having taken off with the leading research organizations, we see this as a natural extension of our platform."

"A couple of leaders in the site sector whom Jason and I both respect immensely brought us together initially" said Barry Lake, Devana Solutions CEO & Co-Founder, "and the prospect of combining BEKHealth's platform with Devana IGNITE's automation of site startup workflows and capture and analytics of trial performance metrics will be revolutionary for Sponsors and CROs seeking predictability and reliability of trial and site performance."

With a joint commercialization agreement in place, BEKHealth and Devana Solutions are already collaborating on client and prospect referrals for demonstrations of the systems for clinical trial stakeholders including site organizations, Sponsors and CROs while the engineers have begun the work of integrating the platforms in advance of a projected rollout of the combined solution in Q4.

Abzena Announces Senior Director of Manufacturing Appointment at Bristol, Pennsylvania facility

Abzena has announced the appointment of Anu Bansal as Senior Director of Manufacturing at its facility in Bristol, Pennsylvania.

With more than 20 years in the biopharmaceutical industry, Bansal has previously held various roles at Genentech, a member of the Roche Group. Prior to joining Genentech, Bansal held various roles at Eli Lilly and Company and at Bristol-Myers Squibb (formerly Dupont Pharmaceuticals Company) across R&D, quality and QC.

Bansal brings with her experience of discovering, developing and licensing both bio and pharmaceutical product for global markets with specific emphasis on managing multiple tech transfers, execution in manufacturing, regulatory submissions, filings, and licensures.

Bansal received her Ph.D. in Molecular Biophysics at UT Southwestern Medical Center in Dallas, Texas and a M.S. in Biochemistry from the University of Delaware.

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"A vaccine for COVID-19 is crucial to overcome the current pandemic, and we appreciate the opportunity to work with AstraZeneca on this important Phase III trial," said Mark Blumling, CEO of Headlands Research.

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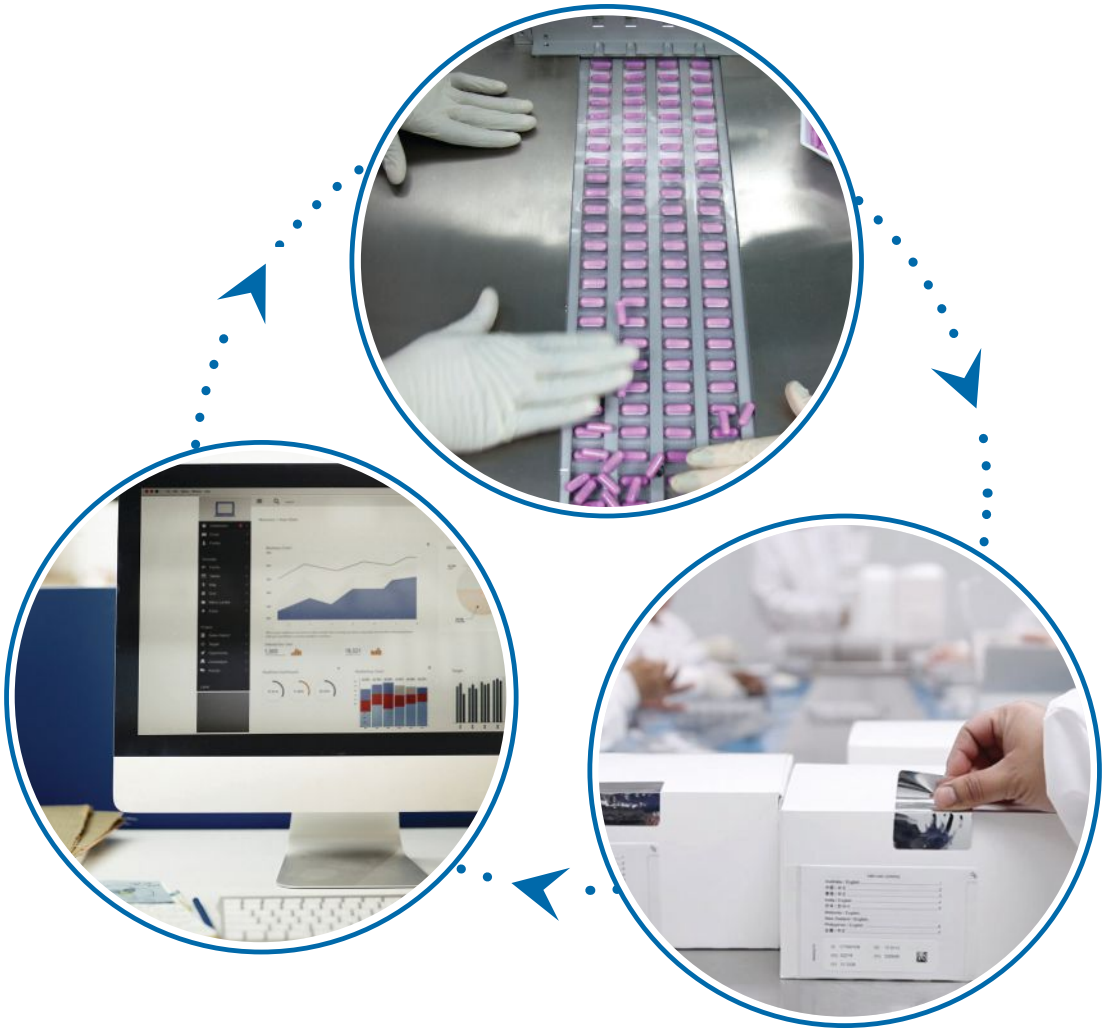

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